OHIO AGRICULTURAL EXPERIMENT STATION

TECHNICAL SERIES, BULLETIN No. 5

A REVIEW OF THE LITERATURE

OF

PHOSPHORUS COMPOUNDS IN ANIMAL METABOLISM

By E. B. FORBES AND M. HELEN KEITH

WOOSTER, OHIO, U. S. A., MARCH, 1914

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PREFACE.

This review of the literature of phosphorus metabolism was undertaken as a part of a general program of experimentation in this field which is being conducted by the Department of Nutrition of this institution.

In our selection of material we have in mind the bearing of this work on practical human nutrition and animal husbandry, and have sought to adapt it to the requirements of the college graduate who has an especial interest in nutrition.

A certain over-emphasis of the subject of this discussion must inevitably result from the restriction of its scope to a consideration of the compounds of but a single element, but we have sought throughout the discussion to maintain correct perspective by indicating the connections of our subject with those matters with which it stands in natural relationship.

Since the compounds of phosphorus have to do, in prominent ways, with all of the life processes of animals, our subject, though narrow in form, might easily be construed to cover the whole field of nutrition. It has been necessary, therefore, in the conduct of this study, arbitrarily to limit its scope in order to render its completion in any way a practical possibility, and we have been obliged entirely to ignore some important divisions of the subject for no better reason than that life is short.

The thoroughness with which we have treated the several sections of this discussion varies much. Our treatment of the field of pathology has been especially incomplete. Here it was our idea to include only such matters as we considered of interest to the student of nutrition in general, and we have not gone into a discussion of diseases, as such, in a way to serve the requirements of the pathologist. We have made no careful search of the literature of pathology for materials on phosphorus metabolism. The whole subject of phosphorus poisoning has been omitted, this matter being considered as quite apart, in reality, from phosphorus metabolism in the usual sense—and the literature is enormous. The relation of phosphatids, especially lecithin, to the action of alkaloids and other drugs, as well as antitoxins, precipitins, hemolysins, bacteriolysins, agglutinins and opsonins is of a special nature, having to do with the maintenance of immunity rather than with phosphorus metabolism in the usual sense, and is not included in this discussion.

Clinical reports are submitted in great brevity and usually without comment. They certainly have a value, but it is impossible to say, in a given case, whether this value be great or small. Some of the reasons for this are as follows:

The first interest of the medical profession is the cure of the patient and not the acquirement of experimental evidence; it is usually impossible to provide proper experimental controls or checks; even in hospitals the environment of the patient does not always constitute a proper basis for exact experimentation; the rights of the patient prevent the full development and realization of such unfavorable results of treatment as might follow under strictly experimental conditions; and the imagination of the patient undoubtedly cuts a figure in symptoms and results which is not characteristic of experiments on animals with less capacity to think.

The chemistry of phosphorus compounds, and the phosphorus compounds of animal bodies and products, and of foods and drugs have been briefly considered with the idea of making clear the bearing of the matter on normal phosphorus metabolism, in which field we have considered all of the material which has come to our attention.

The selection of articles for inclusion in this review was made by the use of indices, supplemented by a page-to-page search of the journals considered as most likely to contain the desired material. The main sources of the articles included are as indicated in the following list, though many references were also taken from scattered sources.

American Journal of Physiology 1 (1898) to 32, (Dec. 1913)
Archiv für die gesammte Physiologie 1 (1868) to 156, 442 (Mar. 1914)
Biochemical Journal 1 (1906) to 7, (Dec. 1913)
Biochemische Zeitschrift 1 (1906) to 59 (Feb. 1914)
Chemical Abstracts 1 (1907) to 8, 1220 (Mar. 20, 1914)
Die Ernährung der landwirtschaftlichen Nutztiere, vierte Auflage; O. Kellner 1907.
Ergebnisse der Physiologie 1 to 13 (1913)
Experiment Station Record (1899) to 29, 899 (Feb. 1914)
Handbuch der Biochemie des Menschen und der Tiere, Carl Oppenheimer, 1908-1913.
International Catalog of Scientific Literature. Q. Physiology 1 to 8 (1911)
Jahresbericht über die Fortschritte der Thierchemie 1 (1871) to 41 (1911)
Journal für Landwirtschaft 49 (1901) to 61 (1913)
Journal of the American Medical Association 34 (1900) to 61 (Dec., 1913)
Journal of Physiology 26 (Dec. 1900) to 47, No. 6 (Feb. 1914)
Metabolism and Practical Medicine, Vols. I, II, III, Carl von Noorden, 1907.
Physiologie und Pathologie des Mineralstoffwechsels, Albert Albu and Carl Neuberg, 1906.
Review of American Chemical Research 6 (1900) to 12 (1906)—last issue.
Revue de la Société d' Hygiene Alimentaire 1 (1904) to 7 (1909) entire.
The Journal of Biological Chemistry 1 (1905-06) to 17, 304 (Mar. 1914)

The Journal of the American Chemical Society 1 (1879) to 36, 616 (Mar. 1914)
Vierteljahreschrift der Nahrungs-Chemie 9 (1894) to 12 (1897) last issue.
Zeitschrift für Biologie 39 (N. F. 21) to 63 (N. F. 45), Heft 9 (Mar. 1914)
Zeitschrift für Kinderheilkunde. Originale 1 (1910-11) to 10, Hefte 1-4 (Feb. 1914)
Zeitschrift für Nahrungs Untersuchung 1 (1898) to 10 (1905)
Zeitschrift für physiologische Chemie 1 (1877) to 89, 324 (Feb. 1914)
Zeitschrift für Untersuchung der Nahrungs- und Genussmittel to 27, 360 (Feb. 1914)

In general we have considered only original articles. Most of the study of the literature has been pursued by a uniform method of preparation of abstracts including (1) the complete reference, (2) the object of the investigation, (3) the methods employed, (4) the nature of the data recorded, (5) numerical results and (6) the author's conclusions in full.

Gross misconceptions have been generally ignored, in consideration of the extreme brevity with which we have been obliged to treat much good material.

We have not gone into a discussion of analytical methods, though they have been considered, and much work has been thrown out because of the use of methods unsuited to the purpose. It is true, however, that much work, known to have been accomplished by faulty methods, has been retained, often because the methods have been fairly satisfactory for comparative purposes, and again, frequently because better methods have not been discovered or have not come into general use. In very few cases, for instance, do the differential estimations of the groups of organic phosphorus compounds rest upon critically established analytical procedures, and even so simple a problem as the determination of inorganic phosphorus in plant and animal substances is still a problem,– fairly well settled for some substances, it is true, but by no means for all from which we report determinations.

Candor requires the observation that much of the work considered is without great value, but until supplanted by results of higher grade we are obliged to give it space. This applies especially to metabolism data, the experiments being, as a rule, much too short to afford safe bases for conclusions; and elaborate discussions of urinary conditions, feces data not being included, are far too common.

Numerical data have been largely retabulated, and very commonly they have been recalculated. If found inconsistent they have usually been thrown out, but have sometimes been corrected, with the author's approval.

In addition to data on phosphorus metabolism, we have also commonly taken from the general studies the data on calcium and nitrogen, since these elements are more prominently involved than others with the metabolism of compounds of phosphorus.

We are glad to acknowledge here the assistance in abstracting received from B. M. Hendrix, Dr. H. W. Houghton, E. C. Lathrop, Grace Mac Leod, Dr. Martha A. Phelps, Dr. J. B. Rieger, Florence C. Sargent, Marion E. Sparks and Dr. G. M. Tucker.

The abstracting has been done in the following institutions: Ohio Agricultural Experiment Station, University of Illinois, Library of Congress, Surgeon General's Library, Library of the Department of Agriculture, New York Academy of Medicine, New York Public Library, Columbia University, Massachusetts Institute of Technology, Boston Medical Library, Harvard Medical Library, Boston Public Library, Harvard University, Boston Natural History Museum, Connecticut Agricultural Experiment Station, Yale University, Cleveland Medical Library and Western Reserve Medical College.

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INTRODUCTION

As agricultural scientists our interest in the mineral elements lies in that larger intermediary metabolism between the soil and the sea which begins with the weathering of the rocks, includes the whole of plant and animal metabolism, and ends with the formation of new rocks.

Throughout this vast sweep of chemical change the mineral elements occupy a unique and dominating position, entering in essential ways into every process, and exerting an influence in metabolism entirely out of proportion to the amounts in which they are involved.

In a large and general way life may be regarded as a coördinated system of responses to electrical stimulation. The ions, and especially the inorganic ions, are the bearers of this electricity, and it is because of this fact that they are able to play a leading role in the direction of the whole process of metabolism.

Among the several inorganic elements involved in animal life phosphorus is of especial interest. No other one enters into such a diversity of compounds and plays an important part in so many functions. Structurally, it is important as a constituent of every cell nucleus and so of all cellular structures; it is also prominent in the skeleton, in milk, in sexual elements, glandular tissue and the nervous system. Functionally, it is involved in all cell multiplication, in the activation and control of enzyme actions, in the maintenance of neutrality in the organism, in the conduct of nerve stimuli, and through its relation to osmotic pressure, surface tension and imbibation of water by colloids it has to do with the movement of liquids, with the maintenance of proper liquid contents of the tissues, with cell movements and with absorption and secretion.

Throughout the intricacies of these processes—in considering the relations of the animal to its food—let it be our point of view that inheritance has furnished the plans, the details and specifications which are to govern the whole course of metabolism; that food builds the structure and maintains its processes, in so far as made possible by the nature and amounts of its constituents; that variability in the composition and functions of the animal body, and excess of capacity in its structures constitute a provision of safety, a means of adaptive response to changes in dietary conditions; that time lends to these adaptations such permanency, in the individual, as to constitute specific effects of foods on the life and structure of

the animal; that these specific effects of foods are, in general, due rather to their limitations than to stimulation of supernormal function; that the nature and possible extent of these effects have been separately determined for each species by the particular conditions, and the *variability* of conditions of life to which, through the ages, they have become adapted, and that in relation to practical animal nutrition our interests are in the highest states of function rather than in irreducible physiological minima, since the whole range of success and profit lies close, and ever closer, to maximum possibilities.

The following discussion attempts no complete picture or continuous account of phosphorus metabolism, but seeks merely to arrange in natural and useful sequence the fragmentary material of which it is composed.

BULLETIN
OF THE
Ohio Agricultural Experiment Station

NUMBER 5 MARCH, 1914

PART I

CHEMISTRY OF ORGANIC COMPOUNDS OF PHOSPHORUS

NUCLEOPROTEINS AND THEIR DERIVATIVES

Place in the Scheme of Chemical Compounds. The facts as to the method of growth of the individual animal lead us almost certainly to the conclusion that the transmission of characters from generation to generation, and the determination of the nature of all cellular growth has as its material basis the chemical structure of the nucleoproteins of the cell. In comparison with the almost inconceivable complexity of composition implied by this idea our knowledge of the chemistry of the nucleoproteins is especially superficial and our methods of study most violent. This field must remain for all time in large part unknown and unknowable, and it is only with the grossest facts as to composition, as made manifest by the destruction of the compounds and the study of the wreckage products that we are here concerned.

Nucleoproteins are those compound proteins which yield protein and nucleic acid on cleavage. Any of the simple proteins may occur in this union; and the number of nucleoproteins is practically unlimited. Of those which are found in natural products the protein has been identified in but very few cases.

Under the action of weak acids or of gastric juice the cleavage of nucleoproteins does not, in most cases, produce a nucleic acid directly; but instead, a protein compound of nucleic acid containing less of protein and, consequently, a larger proportion of phosphorus. It is customary to call these simpler protein compounds of nucleic acids by the name nucleins, and to let the name nucleoprotein apply to the naturally occurring substances which are combinations of nucleins with further protein. Nucleoprotein as defined above includes both of these groups.

The nucleins are decomposed by caustic alkali into protein and nucleic acids. All nucleic acids are rich in phosphorus, and on cleavage yield phosphoric acid, purin bases, a carbohydrate (or carbohydrate derivative) and usually pyrimidin bases.

The paranucleins, or pseudonucleins, are derived from the phosphoproteins (nucleoalbumins) in the same way that nucleins are derived from nucleoproteins, and in certain cases paranucleic acids have been obtained, corresponding to nucleic acids. A. Kossel (1891a), proposed the name paranuclein, and noted that paranucleins differ from true nucleins in not yielding purin. Giertz (1899) says that they may be definitely distinguished from true nucleins in that they readily dissolve in water made slightly alkaline with baryta, and that they are decomposed by excess of baryta with the splitting off of phosphoric acid.

Some have reported the cleavage of nucleoprotein directly, with the separation of nucleic acid, and either protein, or its peptones and amino acids (Altmann, 1889; A. Kossel, 1893; Umber, 1901).

The reader is referred to the following articles for reviews of the work on this subject reported up to the dates of the several papers:—Nolf (1898), Steudel (1907a), Schaumann (1910), Brugsch and Schittenhelm (1910) and Brahm (1913).

Occurrence of Nucleoproteins. Nucleoproteins occur chiefly in the cell nuclei; but they also often occur in the cytoplasm, and are found in the blood serum and other fluids.

They have been obtained most abundantly from those products and organs which are rich in nuclei. The nuclein first discovered was that formed from pus by peptic digestion. This discovery was the work of Miescher. Plósz (1871 and Ibid., p. 441), also obtained a similar substance from the blood corpuscles of a bird and of a snake. Miescher's more extensive study, to which we owe considerable of our knowledge of these compounds, was made upon sperm and spermatozoa, chiefly from salmon. The substance which Miescher (1878, 1896, 1897) called protein-free nuclein was named nucleic acid by Altmann (1899) on account of its acid properties.

The nucleic acids to which the greatest amount of attention has been given are those of the thymus, of spermatozoa and of yeast; and in addition to these we are fairly familiar with those of the pancreas, adrenals, spleen, testes and fish eggs. The only plant nucleic acid besides that present in yeast, which has been much investigated, is that which T. B. Osborne and his associates have isolated from wheat embryo, and have named tritico-nucleic acid (Osborne and Campbell, 1900a; Osborne and Harris, 1902; Wheeler and Johnson, 1903; Mendel, Underhill and White, 1903; Osborne and Heyl, 1908; Levene and LaForge, 1910).

Other early discussions and reports of nucleins besides those of Miescher and of Plósz are those of J. W. Müller (1873), of Piccard (1874) on salmon sperm, of von Jaksch (1876) on nucleins from human brain, and of Klinkenberg (1882) on some nucleins from various seeds used as fodders. As long ago as 1847 Justus Liebig isolated from flesh an acid to which he gave the name inosinic acid, and which he analyzed, but he did not find the phosphorus. In 1878 Schutzenberger (1878) named decomposition products of brewer's yeast, which were such as are now recognized as those of nucleoproteins.

PROPERTIES OF NUCLEOPROTEINS

The nucleoproteins, after isolation and purification, are loose, white powders, insoluble in water, but soluble in alkali solutions by union with the alkali. From such solutions they are precipitated by acids; excess of mineral acids dissolves them, but acetic acid less readily. They are acid in character.

The percentage composition of nucleoproteins is very variable and the determinations doubtful; but all contain phosphorus, perhaps from 0.5 to 3.0 percent. That obtained by Liebermeister (1906) from the blood serum of the horse was very low in phosphorus, only about 0.08 percent.

It has been commonly stated that the nucleoproteins contain iron in organic combination; but the amounts found vary greatly, and the nature of its relation to the molecule, if it be a part of the nucleoprotein molecule, is not known (see S. S. Zaleski, 1886; Hammarsten, 1894; Scaffidi, 1908; Salkowski, 1909a, 1909b; Capezzuoli, 1909a). Salkowski (1909b) finds iron present, but very loosely bound. Ascoli (1899) reports it in plasminic acid, showing relations which he thinks indicate a metaphosphoric combination; but Sauerland (1910) fails to find iron in the free nucleic acids from pancreas and spermatozoa heads, and doubts its existence in the nucleoproteins.

The cleavage products are characteristic constituents. The only attempts which we have noticed, to make complete determinations of all cleavage products are those of Wohlgemuth (1903, 1904a, 1904b, 1905). The nucleoproteins give the color reactions of proteins. So far as examined, they are all dextrorotatory (Gamgee and Jones, 1903a, 1903b, 1903c).

On peptic digestion nucleoproteins yield true nucleins. Weak acids cause decomposition, and the solutions of the alkali combinations are decomposed even by heating with water.

A list of references to nucleoprotein investigations is given below:

NUCLEOPROTEIN STUDIES ARRANGED WITH REFERENCE TO THE SOURCE OF THE NUCLEOPROTEIN

From Thymus: Bang, 1900a, 1900b, 1903 and 1904; Gamgee and Jones; 1903a, 1903b, 1903c; Halliburton, 1895; Halliburton and Brodie, 1894; Huiskamp, 1901a, 1901b, 1903; A. Kossel, 1900; Lilienfeld, 1894; Malengreau, 1900, 1901; Steudel, 1913b.

From Liver: Goubau, 1911; Halliburton, 1892, 1895; Salkowski, 1909a, 1909b; Scaffidi, 1908, 1909a; Wohlgemuth, 1903, 1904a, 1904b, 1905.

From Pancreas: Gamgee and Jones, 1903a, 1903b, 1903c; Hammarsten, 1893, 1894; Jones and Whipple, 1902; Knopf, 1914; Levene, 1904; Levene and Stookey, 1904; Umber, 1900, 1901.

From Suprarenals: Gamgee and Jones, 1903a, 1903b, 1903c; Jones and Whipple, 1902.

From Brain: Halliburton, 1895; von Jaksch, 1876; Levene, 1899.

From Blood Corpuscles: Bang, 1903, 1904; Halliburton, 1895; Halliburton and Friend, 1889; A. Kossel, 1881, 1882; Plósz, 1871.

From Blood Serum: Liebermeister, 1906; Pekelharing, 1895.

From Leucocytes: Bang, 1903, 1904; Lilienfeld, 1894.

From Yeast: A. Kossel, 1879, 1880, 1881.

From Other Sources: Spleen; Capezzuoli, 1909a; Goubau, 1911; Sato, 1909. Thyroid; Oswald, Ad., 1899. Kidney; Goubau, 1911; Halliburton, 1892, 1895. Mammary glands; R. Odenius, 1899. Human Placenta; Bottazzi, 1903; Cocchi, 1901. Testes; Goubau, 1911. Spermatozoa; Steudel, 1911a, 1911b, 1913a. Lymph glands; Bang, 1903, 1904. Muscle; Pekelharing, 1896. Marrow; Halliburton, 1895. Pus; Goubau, 1911; A. Kossel, 1881. Egg-yolk; A. Kossel, 1885, 1886. Several nucleins; Klinkenberg, 1882. Barley sprouts; Petit, 1893. Several seeds; Vorbrodt, 1910.

PROPERTIES OF NUCLEIC ACIDS

Nucleic acids are white, amorphous, acid powders, insoluble in water, but soluble in ammoniacal or alkaline water. Since all of the phosphorus of the nucleoprotein molecule is in the nucleic acid fraction, the percentage here is high, perhaps 8.0-10.0 percent. The nucleic acids precipitate proteins from solution. The affinity for protein is perhaps their most significant property.

Nucleins stand between nucleoproteins and nucleic acids in properties and composition, corresponding with their intermediate position in production.

Feulgen (1912, 1913a,) has prepared, analyzed and studied the properties of compounds of nucleic acid with dyes, the composition of which he thinks is such as to indicate the formation of tetrabasic salts, and he suggests that perhaps nucleoproteins are such saltlike combinations of nucleic acids with the basic proteins. Feulgen says that Bang's work on lymph glands gives support to this conception, and throws doubt on the existence of nucleins.

CLEAVAGE PRODUCTS OF NUCLEOPROTEINS

Outline of the Processes: Hydrolytic cleavages produce from nucleoproteins, simple proteins, carbohydrates, phosphoric acid, and purin and pyrimidin bases, with the intermediate formation of nucleins and nucleic acids, as may be represented by the following scheme:

Nucleoproteins

Proteins — Nucleins

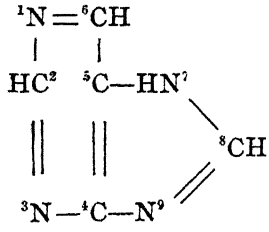
Proteins — Nucleic acids

Carbohydrates	Phosphoric acid	Purin bases	Pyrimidin bases
Pentoses		Adenin	Thymin
Hexoses		Guanin	Cytosin
Unidentified		Hypoxanthin	Uracil
		Xanthin	

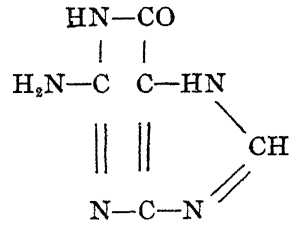
The carbohydrates may appear as formic or levulinic acid. Oxidative processes transform hypoxanthin to xanthin, xanthin to uric acid, and sometimes further oxidize the uric acid (probably allantoin is formed in such a way, and perhaps oxalic acid and urea).

PURIN BASES

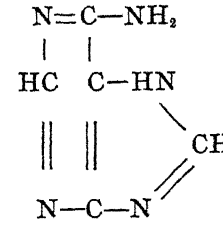
Four purins have been obtained, namely,- guanin, adenin, hypoxanthin and xanthin. These are spoken of also as the nuclein bases, or alloxur bases. The relations of these to one another and to simple purin are indicated by the following structural formulae:



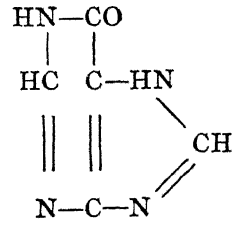
Purin



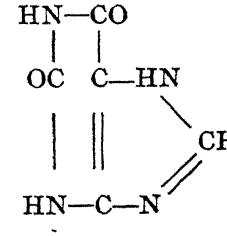
Guanin



Adenin

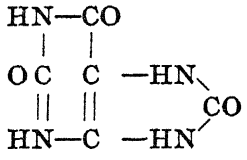


Hypoxanthin



Xanthin

Guanin and adenin contain the amino group (NH_2) while hypoxanthin and xanthin are oxygen derivatives. The figures placed beside members of the purin ring are used to designate the points at which substitutions are made in making up the molecule of the derivatives, and they may be used in designating these derivatives; thus guanin is 2-amino-6-oxypurin, adenin is 6-aminopurin, hypoxanthin is 6-oxypurin and xanthin is 2, 6-dioxypurin. By removal of the amino group guanin becomes hypoxanthin, by removal of amino and introduction of oxygen adenin becomes xanthin, hypoxanthin by oxidation becomes xanthin, and by further oxidation this becomes uric acid, the structural formula of which follows:



Uric acid (2, 6, 8—trioxypurin)

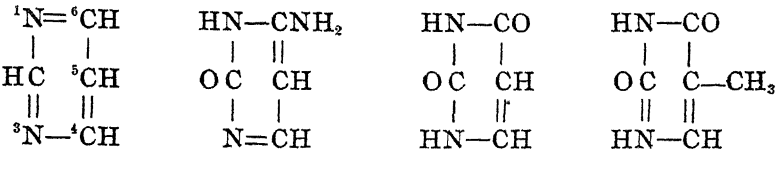
The importance of these purin bases as decomposition products of cell-nuclei and of nuclein was shown by the researches of Albrecht Kossel, and made clear in his repeated discussions. He discovered and named adenin (Kossel, A., 1886), and we have already mentioned the fact that he marked the distinction between nucleins which yield purin bases on cleavage, and those which do not, by naming the latter paranucleins. The processes transforming one of these purins to another and the enzymes causing such transformations have received special attention from Walter Jones.

Jones has pointed out that, since guanin and adenin may so readily be changed into the other bases, it is very probable that, at least in some of the cases, the hypoxanthin or xanthin found among the decomposition products was of such origin, and was not present in the nucleic acid as such. By use of his methods, which control changes of that kind, he was able to prove that the nucleic acids of thymus, spleen and pancreas contain no other purin bases but guanin and adenin, and he concluded that the nucleic acids from these three sources, at least, are identical. (Jones and Austrian, 1907; Jones, 1908; Jones and Whipple, 1902). We recommend to the reader his clarifying discussion (1908) "On the Identity of the Nucleic Acids of the Thymus, Spleen and Pancreas," in which he attempts to interpret and adjust the apparently contradictory findings of various authors as to the identity of nucleic acids and of their decomposition products.

Guanylic acid contains but one purin base, namely guanin; and inosinic acid, likewise only one, hypoxanthin.

PYRIMIDIN BASES

Three pyrimidin bases have been obtained from nucleic acids,—cytosin, uracil and thymin. The relations of these to one another and to pyrimidin are expressed in the graphic formulae as follows:



Pyrimidin	Cytosin, 6-amino-2-oxy-pyrimidin	Uracil, 2, 6-dioxy-pyrimidin	Thymin, 5-methyl-uracil

The ring nucleus of these compounds is simpler than that of the purins, but might readily be made from that in case of decomposition, as may be seen by inspection of the graphic formulae.

Each of these compounds was first prepared in Kossel's laboratory (A. Kossel and A. Neumann, 1893, 1894; A. Kossel, 1894; Ascoli, 1900b), and has been further studied there as well as elsewhere.

All three of these bases are in some of the nucleic acids, though thymin and cytosin are most common. In some cases where uracil has been obtained it was probably a secondary product derived from cytosin. By some it has been held, also, that all of the pyrimidins are secondary products derived from purins (Burián, 1907b); but that idea seems to be satisfactorily disproved, at least as to its universal application, by the work of Steudel (1905b, 1907e), and by T. B. Osborne and Heyl (1908) with regard to tritico-nucleic acid. This last acid (from wheat embryo) and yeast nucleic acid contain only cytosin and uracil. Wheeler and Johnson (1903) showed the cytosin from this acid and that from spleen nucleic acid to be identical. Only the simplest of the nucleic acids, guanylic and inosinic acids, are without pyrimidin bases, so far as is known. The expression thymonucleic acids is sometimes used as a group name for such as contain thymin, and that seems to be practically all of those of animal origin.

CARBOHYDRATES

Among the cleavage products of all true nucleic acids or nucleins are carbohydrates or their derivatives; but the specific identification of the carbohydrate contained in the nucleic acid molecule

has not generally been made. Kossel and many others have found both a pentose and levulinic acid, which latter is a hexose derivative. All the thymonucleic acids (from animal organs) give evidence of some kind of hexose (they yield levulinic acid as a hexose derivative); while the vegetable nucleic acids (yeast nucleic acid and triticonucleic acid from wheat embryos) and guanylic and inosinic acids contain a pentose. Boos (1909), however, in reinvestigating the question of yeast nucleic acid finds indication that it contains no pentose. When pentose as well as hexose has been obtained from the acids derived from animal organs (Levene 1903a; Wohlgemuth, 1903, 1905) it may have been due to an admixture of guanylic acid. F. Bauer (1907) considers that the pentose of inosinic acid is racemic arabinose, while Neuberg and Brahn (1907) and Haiser and Wenzel (1909) and Wohlgemuth make it a laevo-xylose, and Levene feels that he disproved both of these ideas, and proved that the pentose in every case is a dextro-ribose (Levene and Jacobs, 1909b, 1909c).

INTERMEDIARY PRODUCTS

By partial cleavage several workers have obtained various decomposition products from nucleic acids which are thought to be of especial interest as throwing light on the makeup of the more complex compound.

Frequently the purin bases split off first, but not with sufficient ease to indicate that they were in salt-like combination. Alsberg (1904) isolated what he called heminucleic acid, containing only one-half of the purin bases, and Kossel and Neumann (A. Kossel, 1894; A. Kossel and A. Neumann, 1896) obtained an acid free from all the purin bases, without loss of phosphoric acid, by boiling thymus nucleic acid with water. This second acid was called thymic acid, and it has received considerable attention, owing to the suggestion that it might bear the same relation to paranucleins that the nucleic acids bear to true nucleins. Milroy (1896) proved that thymic acid is not identical with paranucleic acid by showing that synthetic compounds of thymic acid with proteins, though much like the natural paranucleins, do not give the same acid on cleavage. Steudel and Brigl (1911) obtained the same, or a similar thymic acid, by nitric acid oxidation of the thymus nucleic acid.

A. Kossel (1894), A. Neumann (1898, 1899), and Kostytschew (1903) found three other modifications of nucleic acid from the thymus gland which they called α-nucleic acid, β-nucleic acid and

nucleothyminic acid, these differing from one another in the amount of nuclein bases present, and showing certain differences in properties.

Alsberg (1904) also obtained, on more energetic cleavage, an acid free from all its purin bases and from phosphorus, which he called nucleotin, and which corresponds with Schmiedeberg's (1900) idea that the ground substance of nucleic acids is a nucleotin-phosphoric acid which is combined in some way with purin bases. The thymic acid of Kossel and Neumann and the thymin-glucophosphoric acid of Levene and Mandel (1908a) would be such nucleotin-phosphoric acids.

Under the influence of enzyme action or nitric acid oxidation Steudel (1908a) obtained, from nucleic acid, products in which the sugar was in organic union with phosphoric acid after the purin bases were removed. This investigation of Steudel's also made evident that the purins were closely bound to the carbohydrate section of the nucleic acid; and the same relationship is indicated by the isolation and the synthesis of compounds of the carbohydrates with purin and pyrimidin bases which have been made by Levene and his associates. Levene, however, has not succeeded in forming them by such cleavage as that of Steudel mentioned above.

The union with the carbohydrate, at least in the case of purin bases, is said to be glucoside-like, and the compounds are called nucleosides. Jones (1911b) showed that enzyme cleavage sometimes forms such bodies by splitting off phosphoric acid from nucleic acids.

Under special conditions Jones (1912) and Jones and Richards (1914) have obtained a simple nucleic acid, guanylic acid, from the complex nucleic acids of pancreas and of yeast.

Considering all of these intermediary products, it seems evident that the purins are more easily separated by cleavage than the pyrimidin bases, that the purin cleavage is gradual, that the phosphoric acid may be as easily separated as at least a part of the purin bases, and that the carbohydrates never split off so as to leave the purin and pyrimidin bases united with phosphoric acid. By mild acid hydrolysis phosphoric acid is more readily split off from purin than from pyrimidin union.

MONONUCLEIC ACIDS

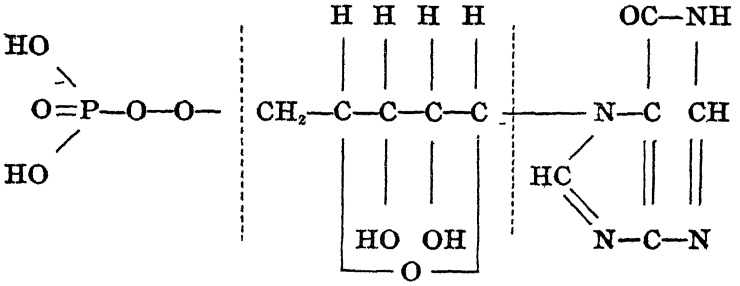
It is convenient to distinguish between nucleic acids containing only one base, which may be called mononucleic acids, or simple nucleic acids, and those which contain more bases, and which may be

called polynucleic acids, or complex nucleic acids. The latter are the ordinary nucleic acids, and may be looked on as combinations of the simple acids (usually four such). Levene calls the two groups, whether natural or artificial, mononucleotides and polynucleotides.

Jones (1912) and Jones and Richards (1914) have succeeded in cleaving a polynucleotide, yeast nucleic acid, so as to obtain a mononucleotide, guanylic acid, from it; and the work of Feulgen (1913b) and of Knopf (1914) suggests that Hammarsten's method of preparing guanylic acid from the pancreas may involve a like process.

INOSINIC ACID

An acid yielding on hydrolysis only phosphoric acid, hypoxanthin and a pentose, and named inosinic acid, is found in meat extracts. It was isolated by Liebig (1847), but the formula then given does not include phosphorus. It is agreed that this is a simple acid containing but one molecule of each component. It is, therefore, what Levene calls a mononucleotide. The empirical formula is $C_{10}H_{13}N_4PO_8$, but several structural formulae have been suggested. The work of Levene and Jacobs seems to have proved that the linking is such as to include the pentoside inosin, made up of hypoxanthin and the pentose. Similar formulae are given by Levene and Jacobs and by Haiser and Wenzel; one which the former authors suggest is given below, the purin being bound to the sugar in the glucoside manner, and the phosphoric acid in ester manner:



Phosphoric acid **Pentose** **Hypoxanthin**

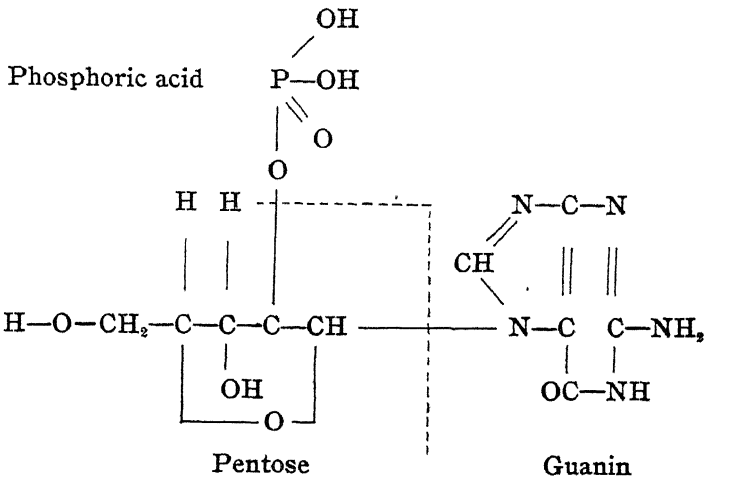
(See Haiser, 1895; F. Bauer, 1907; Neuberg and Brahn, 1907; Levene and Jacobs; 1908, 1909a, 1909b, 1911a; Haiser and Wenzel, 1909.)

GUANYLIC ACID

Bang discovered in the pancreas of the ox a nucleic acid yielding no base but guanin, and he named it guanylic acid. He at first thought glycerin was present, but that idea was not confirmed. The carbohydrate found was shown to be a pentose, and the relation of

N:P, that of 5:1. In his latest reports he gives the formula $C_{44}H_{65}N_{20}P_4O_{34}$, and speaks of the molecule as made up of 4 guanin, 4 pentose and 4 phosphoric acid groups, together with some unidentified substance not containing nitrogen or phosphorus. (Bang, 1898, 1901a, 1901b; Bang and Raaschon, 1903; Bang, 1908, 1910a, 1910b.)

Steudel and Brigl (1910), however, and Levene and Jacobs (1909c, 1909e, 1912c) are inclined to give to guanylic acid a formula and structure more like that of inosinic acid. According to them the empirical formula is $C_{10}H_{14}N_5O_8P$. Levene and Jacobs (1912c) find some reason to think the structure is not identical with that of inosinic acid, and give the structural formula as follows:



The phosphoric acid is cleaved from guanylic acid more readily than from inosinic.

Guanylic acid has been found at least in the pancreas, the spleen, the liver and milk glands. (Steudel 1907d; von Fürth and Jerusalem, 1907, 1908; Jones and Rowntree, 1908; Levene and Mandel, 1908b; R. Odenius, 1899.) Jones (1912) has produced it from yeast nucleic acid. See also Jones and Richards (1914).

The suggestions of an adenylic acid, corresponding to guanylic, have apparently been made on insufficient evidence (A. Kossel and A. Neumann, 1894; Bang, 1904).

POLYNUCLEIC ACIDS

General Similarities. The numerous nucleic acids of animal origin containing both purin and pyrimidin bases, which have been investigated, show striking similarities, and very likely many of them are identical. It is supposed that as a rule they consist of phosphoric acid, adenin, guanin, 2 (or 3) pyrimidin bases, and a hexose, the definite nature of which is not determined. The plant

polynucleic acids which have been studied contain pentose in place of hexose. Levene and LaForge (Levene, 1909b; Levene and LaForge, 1910) find the pentose of both yeast nucleic acid and triticonucleic acid to be d-ribose, and that these acids yield the same products on partial hydrolysis. Therefore they think that these acids are identical. It is customary to think of these complex acids as made up on the basis of four phosphorus atoms to the molecule.

For convenience, a general list of references to studies of these nucleic acids is given here, grouped with reference to their source.

NUCLEIC ACID STUDIES ARRANGED WITH REFERENCE TO THE SOURCE OF THE NUCLEIC ACID

From Thymus: Altmann, 1889; de la Blanchardière, 1913; Burián, 1904a, 1904b, 1907a; Herlant, 1900; Iwanoff, 1903; Jones, 1908; Jones and Austrian, 1907a; Kossel, A., 1894; Kossel, A., and A. Neumann, 1893, 1894, 1896; Kostytschew, 1903; Levene and Mandel, 1908a; Levene and Jacobs, 1912a, 1912b; Neumann, Albert, 1898,1899; Steudel, 1904, 1905a, 1905b, 1907b, 1907c, 1907d, 1908a, 1908b, 1912, 1913b; Tscherniorutzky, Helene, 1912b.

From Spermatozoa or Sperm: Alsberg, 1904; Altmann, 1889; Herlant, 1900; Inouye, 1904, 1906; Kossel, A., 1896; Levene and Mandel, 1906c; Miescher, 1878, 1896, 1897; Noll, 1898; Sauerland, 1910; Schmiedeberg, 1900; Steudel, 1906a, 1906b, 1907b, 1907c, 1907d, 1911a.

From Spleen: Bang, 1903, 1904; Inouye, 1904; Jones 1908; Levene, 1901b, 1903a, 1903b, 1904, 1905; Levene and Mandel, 1906a.

From Pancreas: Feulgen, 1913b; Jones, 1908; Levene, 1901b, 1903a, 1903b, 1903d, 1904; Levene and Jacobs, 1909c, 1909e; Sauerland, 1910; Steudel, 1907f; von Fürth and Jerusalem, 1907.

From Testes: Inouye, 1904; Levene, 1903f, 1904.

From Fish Roe: Levene, 1901b; Levene and Mandel, 1906b; J. A. Mandel and Levene, 1906b; Tschernorutzky, Helene, 1912a.

From Yeast: Altmann, 1889; Ascoli, 1899, 1900b; de la Blanchardière, 1913; Boos, 1906, 1909; Burián, 1904a, 1904b, 1907a; Herlant, 1900; Jones, 1912; Jones and Richards, 1914; Kowalevsky, 1910; Levene, 1901b, 1903d, 1909b; Levene and Jacobs, 1909c, 1909f, 1909g, 1910, 1911b; Levene and La Forge, 1912; Liebermann, 1888b, 1889, 1890; Liebermann and Bitto, 1893; Tschernorutzky, Helene, 1912b.

From Wheat Embryo: Levene and La Forge, 1910; Osborne, T. B., and Campbell, 1900a; Osborne, T. B., and Harris, 1902; Osborne, T. B., and Heyl, 1908; Wheeler and Johnson, 1903.

From Brain: Levene, 1899, 1903c, 1903f, 1904.

From Liver: Levene, 1903e; Levene and Jacobs, 1909c.

From Kidney: J. A. Mandel and Levene, 1906a.

From Intestinal Tissue: Araki, 1903b; Inouye and Kotake, 1905.

From Mammary Glands: Basch, 1898; Löbisch, 1906; J. A. Mandel and Levene, 1905.

From Human Placenta: Kikkoji, 1907b.

From Leucocytes: Ascoli, 1900a; A. Kossel, 1893.

General Work: Levene, 1903c, 1910; Levene and Medigreceanu, 1911b, 1911c, 1911d; Schmiedeberg, 1907.

Elementary Composition. Since these compounds are in themselves so complex, and, moreover, always exist, whether in the body or in the food, in conjunction with undetermined proportions of

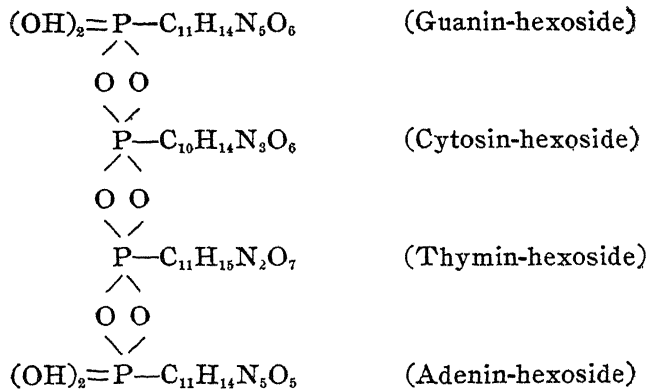
other compounds, and since it is quite doubtful whether they have ever been examined either in a pure condition or in their natural state, it seems that the percentage content of phosphorus or other constituents has no especial significance other than as contributing to a knowledge of the formulae, and then only as an aid to the study of the structure as indicated by chemical reactions and cleavage products. The question of the percentage composition of the proteins which are united to the nucleic acids is practically untouched. On account of such interest as they may possess, a few empirical formulae of nucleic acids are presented. They are determined in part by analysis and in part by probable structure.

FORMULAE OF A FEW NUCLEIC ACIDS

Nucleic acid	Investigator	Date and reference	Empirical formula
Acid from salmon milt	Schmiedeberg	1900	$C_{40}H_{56}N_{14}P_4O_{26}$
Thymus nucleic acid	Steudel	1912	$C_{43}H_{61}N_{15}P_4O_{34}$
Yeast nucleic acid	Levene	1909b	$C_{38}H_{49}N_{15}P_4O_{29}$
Yeast nucleic acid	Kowalevsky	1910	$C_{29}H_{42}N_{13}P_3O_{23}$
Triticonucleic acid, (from wheat embryo)	Osborne and Harris	1902	$C_{41}H_{61}N_{16}P_4O_{31}$

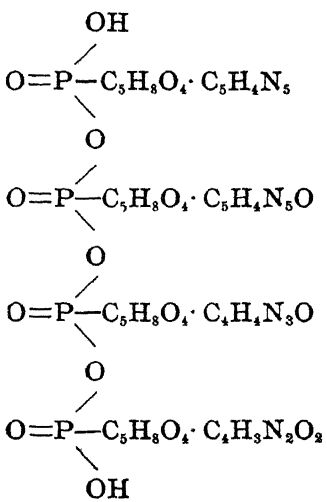
Structure. Two extensive investigations which have led to somewhat definite pictures of the structure of these nucleic acids are those of Steudel and of Levene and his collaborators. With regard to the principal thymus nucleic acid (and Steudel thinks that from herring sperm is identical with this) these authorities are agreed that the molecule contains the four bases guanin, adenin, thymin and cytosin in unimolecular relation, and each bound to a hexose molecule which in turn is bound to phosphoric acid, there being four phosphoric acid molecules; also that the linking of the hexose with the purin bases (and perhaps that with pyrimidin bases) is glucoside-like, but the union with pyrimidins is much less easily broken than that with purins. Steudel's picture involves a more condensed form of phosphoric acid than Levene's. Levene, applying the name mononucleotide to the individual complexes of a single base, carbohydrate and phosphoric acid, which he considers quite analogous to inosinic and guanylic acids (see the graphic formulae given), looks upon these acids as polynucleotides made up of four mononucleotides. Jones (1912) has brought about a cleavage of yeast nucleic acid with the production of the mononucleotide, guanylic acid. Steudel's formula does not attempt to represent the linking within the hexose, nor in the base-hexoside.

Steudel's (1912) formula for thymus acid is:

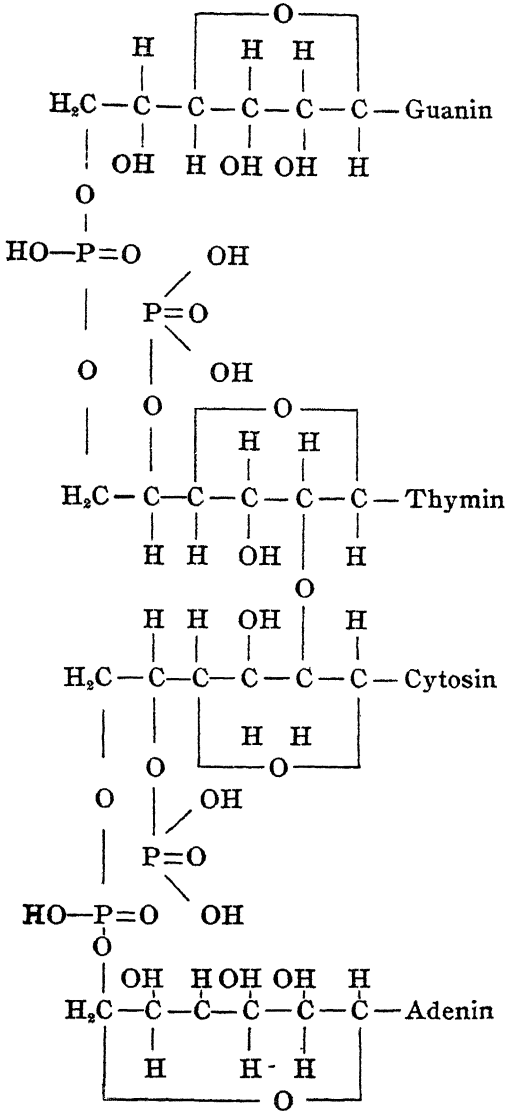


In Levene and Jacobs's formula (p. 27) the two pyrimidin-nucleotides are represented as linked to each other by their sugar, while the phosphoric acids of the purin-nucleotides serve to link the purin-nucleotides with the sugar (not the phosphoric acid) of the pyrimidin-nucleotides. These conceptions correspond with the intermediary products obtained.

From yeast nucleic acid Levene and Jacobs (1909f, 1909g, 1910, 1911b) find the phosphoric acid more readily cleaved and the purins less readily than from thymus nucleic acid, and the structural formula suggested is:



Levene and Jacob's (1912b) formula for thymus nucleic acid is:



Levene's ideas as to the structure and cleavage of nucleic acids, together with the distribution of cleaving enzymes in the animal body were clearly summarized by Levene and Medigreceanu (1911d). See Ferments of Individual Organs.

Helene Tschernorutzky is making a study of the glucoside relation in these acids by attempting cleavage by means of enzymes which are known to have the power to split glucosides. So far the

evidence is unfavorable, for the work reported in August, 1912 (Tschernorutzky, H., 1912b) resulted in a separation of inorganic phosphate as well as purin bases, indicating a more thoroughgoing cleavage, a nuclease action.

Burián (1904a, 1904b, 1907a) believes the purin bases to be linked to the remainder of the nucleic acid at the 7-place of the purin ring. Levene thinks that the pyrimidins are linked at either the 3- or the 4- place. (Levene and LaForge, 1912).

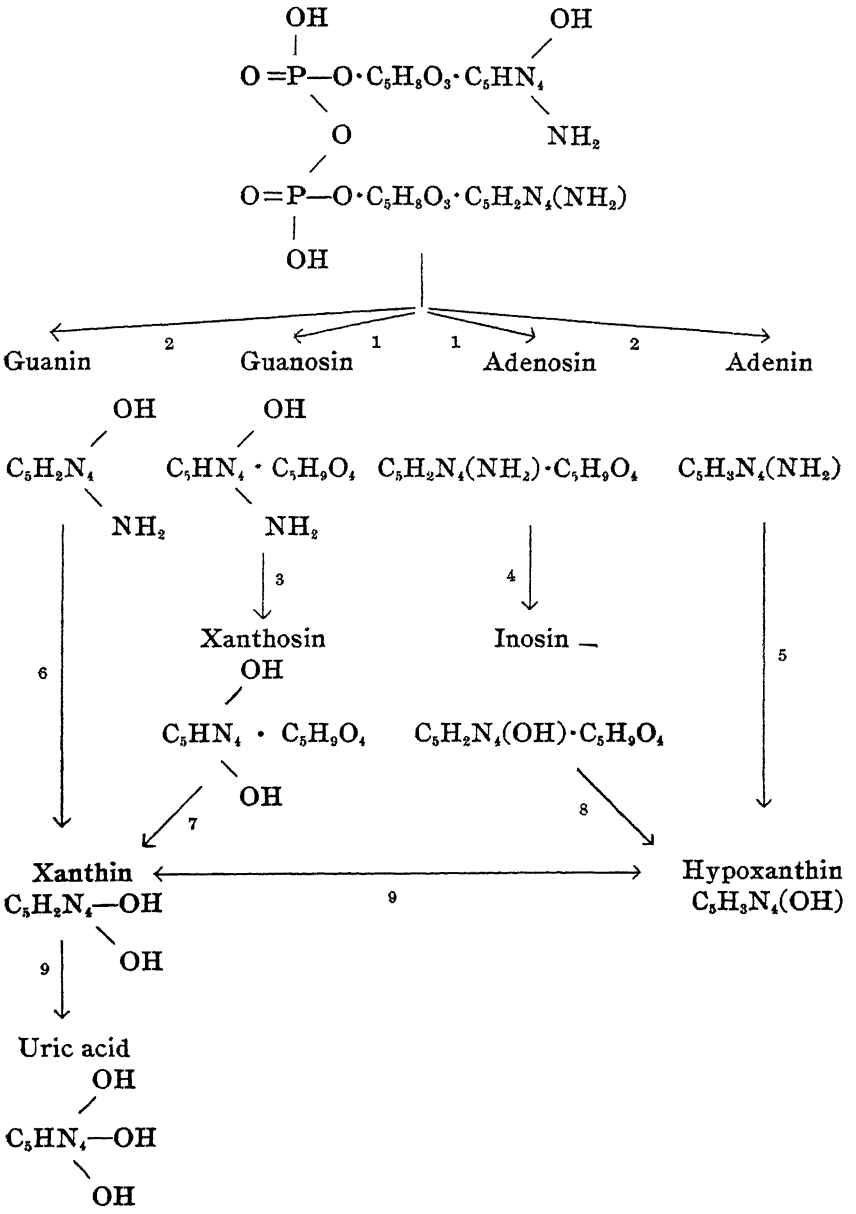
ENZYMES CONCERNED IN NUCLEIC ACID CLEAVAGE

The name nuclease has been used to signify an enzyme which brings about complete disruption of the nuclein molecule. It was first applied by Iwanoff (1903). Evidence of such an enzyme (or enzymes) has repeatedly been found in aqueous extracts of animal organs (Jones, 1904a, 1904b; Levene and Medigreceanu, 1911b, 1911d); but it is probable that the process is due to several enzymes acting in succession.

Jones distinguishes four enzymes having the power to deaminize, two of which, guanase (Jones and Partridge, 1904) and adenase (Jones and Winternitz, 1905), act directly on the purin bases (guanin and adenin, respectively), and two on the glucosides of these bases (guanosin-deaminase converting guanosin to xanthosin, and adenosin-deaminase converting adenosin to inosin, the hypoxanthin glucoside) (Jones, 1911b). Accordingly he recognizes two general paths by which the nucleic acid may be transformed for the formation of uric acid; (1) a nuclease may cleave off the phosphoric acid and the carbohydrate, leaving the purin (and the pyrimidin) bases, the purin bases then being transformed by the deaminizing ferments guanase and adenase into xanthin and hypoxanthin, respectively, the hypoxanthin being oxidizable to xanthin, and xanthin to uric acid through the agency of xanthoöxidase; or (2) the nucleic acid may first be broken down by a cleavage of phosphoric acid only, by which guanosin and adenosin are left, and they may be deaminized at once into xanthosin and inosin, and then have their carbohydrates cleaved off, with the formation of xanthin and hypoxanthin; or the carbohydrates may break off before deaminization, which would transform them to guanin and adenin, upon which guanase and adenase act as in the other line of cleavage; in either case the xanthoöxidase completes the process. The following diagramatic scheme taken from Amberg and Jones (1911b) may help to make this clear. The arrows indicate possible changes, for each of which a distinct ferment might be required. The numbered ones have been proved to be present in one or more organs or fluids.

DIAGRAMATIC SCHEME OF POSSIBLE CLEAVAGES OF NUCLEIC ACID AND THE TRANSFORMATIONS RESULTING IN THE FORMATION OF URIC ACID

Nucleic acid, shown as dinucleoside



Enzymes represented:

1. Phosphonuclease—cleaving off phosphoric acid.
2. Purin nuclease—cleaving off purins.
3. Guanosin deamidase—removing amino group (NH_2) of guanosin.
4. Adenosin deamidase—removing amino group (NH_2) of adenosin.
5. Adenase—removing amino group of adenin.
6. Guanase—removing amino group of guanin.
7. Xanthosin hydrolase—hydrolyzing xanthosin, removing carbohydrate.
8. Inosin hydrolase—hydrolyzing inosin, removing carbohydrate.
9. Xanthooxidase—oxidizing hypoxanthin or xanthin to uric acid.

By the terminology of Levene and Medigreceanu (1911d) such nucleic acids as the above would be called "dinucleotides," the simplest of polynucleotides, and the first enzymatic process (brought about by "nucleinases") is the cleavage of polynucleotides to simple nucleotides. The enzymes cleaving these nucleotides, such as Jones calls phosphonucleinase, Levene and Medigreceanu call nucleotidases, and the glucosides resulting they call "nucleosides." The enzymes causing the cleavage of nucleosides are named "nucleosidases."

STUDIES ON ARTIFICIAL NUCLEIN SYNTHESIS

Nucleins have not been made artificially. A number of workers have, however, succeeded in bringing about synthesis of organic compounds of phosphoric acid which seem to resemble in their make-up fractions of the nuclein molecule, and certain of them have been called nucleins. None of these, so far as we have learned, are unions of the phosphoric acid with both carbohydrate and nitrogenous components, and therefore they have not even all the constituents of the nucleic acids. The processes which have been observed may be looked on as partial syntheses of nucleins, for phosphoric acid unions have been made with carbohydrates on the one hand, and with simple proteins on the other.

Apparently direct union of simple proteins with phosphoric acid radicals occurred in the studies of Pohl (1889), of Liebermann (1888b), of Fuld (1902a), and perhaps of Malfatti (1892, 1893). In all of these cases metaphosphoric acid or its salt was used. Bechhold (1901) reports a similar compound of orthophosphoric acid with albumin formed by use of phosphorus oxychloride. Such

compounds as these were, at the time they were made, looked upon as synthetic nucleins (or paranucleins). Giertz (1899) definitely proved that in such a compound as Liebermann's the phosphoric acid does not bear the same relation to the albumin that it does in the natural paranuclein from casein. We now know that even the paranucleins are not made up simply of phosphoric acid and albumin.

Nucleic acids readily precipitate proteins from solution, and, according to the investigation of Milroy (1896), there are then formed firm chemical compounds which somewhat resemble nucleins. Those formed from thymic acid and protein were not identical with natural paranuclein.

By methods similar to that of Bechhold, but carried out at low temperatures, Neuberg and his associates (Neuberg and Pollak, 1910a, 1910b, 1910c, 1910d; Neuberg and Kretschmer, 1911) have succeeded in forming phosphate compounds with the carbohydrates saccharose, glucose, fructose, maltose, lactose and galactose, with glycerin and also with the phosphorus-free proteins lactalbumin and serum globulin. These phosphorized proteins are said to resemble casein in elementary composition and in behavior, in so far, at least, that the first cleavage produced in tryptic and in peptic digestion seems to correspond to the digestion of casein as described by Salkowski (1899, 1901). The authors consider the phosphoric acid to have entered into the protein molecule by uniting with the amino- or imino- group of the protein to form a substituted phosphaminic acid.

Carbohydrate-phosphoric acid esters have frequently been produced in recent years in connection with yeast fermentation of sugars, the union apparently being effected by a ferment present in the yeast. These complexes act as catalytic agents in accelerating the fermentation by yeast or yeast-juice, and it is thought that their formation and subsequent hydrolysis furnish the mechanism by which the well-known favorable influence of phosphates in such fermentation is exerted. Von Lebedew and Griaznoff (1912) give a definite picture of the process as they conceive of it. The extensive work of Young and Harden, of von Lebedew, and of Euler and his associates is especially to be noted. (See Wróblewski, 1901; Iwanoff, 1907; A. Harden and Young, Proc. Chem. Soc. **21** (1905), 189; A. Harden and Young, 1906, 1908a, 1908b, 1909, 1910, 1911a, 1911b; Young, 1907, 1909, 1911; A. Harden, 1910; A. Harden and Norris, 1910; von Lebedew, 1910a, 1910b, 1911a, 1911b, 1911c; Euler and Fodor, 1911; Euler and Lundeqvist, 1911; Euler and Kullberg, 1911a, 1911b; Euler and Ohlsén, 1911, 1912; Harden and Young, 1912; Euler, 1912a, 1912b, 1913; Euler and Bäckström, 1912;

Euler and Funke, 1912; Euler and Johansson, 1912a, 1912b, von Lebedew, and Griaznoff, 1912.) Young identified his compound as a diphosphoric acid ester of the hexose fructose, and others confirm this finding of a diphosphoric ester. Euler has given much attention to the enzyme involved, which he names "phosphatese." Euler and Johansson (1912b) find that neither glycerol, inositol, mannitol nor alanine forms such an ester with phosphates, nor do glucose, fructose and mannose till after they have been altered in some way by an enzyme or by dilute alkali. Von Lebedew and Griaznoff find that dioxyacetone forms an ester with phosphate but glycerin aldehyde does not. According to their conception the yeast fermentation of glucose first cleaves the sugar into these two compounds and then the latter ferments directly; the former by way of the intermediate phosphate ester formation.

Langheld (1910, 1911, 1912) has synthesized first meta- and from them orthophosphoric acid esters from the alcohols. Among his products is a monoester of fructose which he thinks may be identical with the hexose compound of Young and of von Lebedew.

These synthetic investigations will probably give valuable evidence, though indirect, as to the structure of the natural organic phosphorus compounds and as to the anabolic processes which may go on in the animal body.

THE PHOSPHORUS OF NUCLEOPROTEINS

Probably all of the phosphorus of the nucleoproteins is contained in the nucleic acid fraction, and as has been shown, it is there present in a highly oxidized state and apparently ready formed as phosphoric acid, more or less dehydrated, or else as esters of orthophosphoric acid. If, therefore, the natural substances, the nucleoproteins, are completely digested, they yield phosphoric acid; and if only partially digested, the phosphorus is left in the form of substances, nucleins or nucleic acids, which may or may not be of direct use in the body. The question of the extent to which digestive cleavage does take place will be considered in the discussion of metabolism of nucleoproteins.

CHEMISTRY OF PHOSPHOPROTEINS

CASEIN

Our treatment of the literature on the chemistry of casein is by no means exhaustive. Our earliest note is of a discussion by Braconnot in 1830. Since that date there have been probably a thousand articles on this subject. For general reviews see Fuld (1902b) and Raudnitz (1903).

NATURE OF THE COMPOUND

Casein is a phosphoprotein. The recommendations made in 1908 by the joint committee of the American Physiological Society and the Society of Biological Chemists place phosphoproteins among the conjugated proteins and define them as "Compounds of the protein molecule with some, as yet unidentified, phosphorus-containing substance other than a nucleic acid or lecithins," adding "they are possibly esters of some phosphoric acid or acids and protein." The earlier view which looked on them as simple proteins and used the names nucleoalbumin or phosphoglobulin is thus discarded.

Plimmer (1913b), judging from the comparative instability toward alkali hydrolysis, thinks that the phosphoproteins are not esters, and that the phosphorus is probably combined with one of the amino-acids.

Phosphoproteins differ from nucleoproteins in not yielding purin bases on cleavage, and therefore not containing true nucleic acids. Incomplete peptic digestion does, however, leave a phosphorized body resembling the nucleins, which are derived in the same way from nucleoproteins. The residues from phosphoproteins are called para- or pseudonucleins. All the attempts that have been made to isolate a paranucleic acid from paranuclein have failed in that the product obtained still contained protein. Levene and Alsberg (1901) reported such an acid from the paranuclein of ovovitellin, as also did Salkowski (1901), Reh (1908) and M. Dietrich (1909) from the paranuclein of casein. Salkowski examined his preparation in the form of an iron compound, Reh as a uranyl compound, and Dietrich separated four calcium preparations. Reh thought his compound corresponded with a uranyl ammonium phosphate in which the ammonium was replaced by an albumose complex bound in a manner more or less ester-like but not like a salt, and he calls it a polypeptid phosphoric acid. The formula given for the uranyl ester is $C_{29}H_{56}N_8P_2U_2O_{24}$. Dietrich speaks of his compound as a phosphorus-containing casein peptone.

OCCURRENCE OF CASEIN

Casein occurs only in the milk of mammals. It forms the main part of the curd of milk. (For table of casein contents of the milk of different species consult index.) The amount in cow's milk is usually given as not far from 3 percent, while that of human milk is, by most observers, put as low as 1 percent, or even lower. In this respect the milks of the goat, pig and elephant seem to be nearly like that of the cow, those of the ass and mare nearly like that of woman, while those of the buffalo, dog, cat, ewe, and guinea pig have higher casein content than that of the cow.

In milk the casein is in suspension in combination with calcium and perhaps calcium phosphate. According to Lindet (1913a, 1913b) there are two caseins in milk which may be distinguished by their action on polarized light. The solubility of both in the milk is favored by the presence of phosphates and citrates.

ELEMENTARY ANALYSIS AND EMPIRICAL FORMULA

The table below shows the elementary analysis of casein from cow's milk as reported by different authors and the second table similar analyses of casein from the milk of different species.

ELEMENTARY ANALYSIS OF CASEIN FROM COW'S MILK—Percent

Author quoted	Date and reference	C	H	N	S	P	O	
Makris	1876	53.622	7.422	14.20				
Hammarsten	1883, 1885a	52.96	7.05	15.65	0.758	0.847	22.78	Mean results from many substances.
Chittenden and Painter	1885					0.88 0.85		Seven samples
Bechamp	1893					0.752		Mean of four determinations
Von Szontagh	1893					0.87		
Hempel (Lehmann's work)	1894	54.00	7.04	15.6	0.771	0.847		Computed to ash-free basis
Wróblewski	1894a, 1894b	53.00	7.00	15.70	0.80	0.85	25.65	
Osborne, Thomas	1902					0.86		
Storch	1902	53.00	6.4	15.7	0.80	0.85	22.65	Quoted by Mann, Chemistry of Proteids
Ellenberger	1902	53.07	7.13	15.64	0.76	0.8		Taken through Tangl, 1908
Burow	1905	52.825	7.095	15.64	0.725	0.808	22.906	
Tangl	1908	52.69	6.81	15.65	0.832	0.877	23.14	
Kikkoji	1909					0.86±		
Van Slyke and Bosworth	1912, 1913a	53.50	7.13	15.80	0.72	0.71	22.08	Ash only 0.06 percent

ELEMENTARY ANALYSIS OF CASEIN FROM DIFFERENT KINDS OF MILK—Percent

Source of milk	Author quoted	Date and reference	C	H	N	S	P	O
Cow	Summarized from previous table	....	53.00	7.00	15.7	0.8	0.86	22.8
Woman	Makris	1876	52.353	7.266	14.650	....	....	.....
"	Wróblewski[1]	1894a, 1894b	52.24	7.325	14.97	1.117	0.679	23.66
"	Wróblewski[2]	1894a, 1894b	52.41	7.28	15.03	1.11	0.651	.....
"	Bergell and Langstein[3]	1908	52.82	7.04	14.47	0.78	0.26	.....
"	Langstein and Edelstein[4]	1910	52.51	7.07	14.61	0.731	0.243	.....
Buffalo	Tangl	1908	52.88	7.81	15.78	0.833	0.773	21.925
Ass	Storch	1902	54.	7.0	14.4	0.84	1.04	23.32
Ass	Tangl	1908	52.57	7.01	16.28	0.588	1.057	22.495
Sheep	Tangl	1908	52.92	7.05	15.71	0.717	0.809	22.794
Goat	Burow[5]	1905	52.805	7.02	15.64	0.718	0.815	23.002
Goat	Tangl	1908	52.90	6.86	15.48	0.700	0.760	23.300
Rabbit	Burow[5]	1905	52.866	7.045	15.595	0.733	0.810	22.952
Mare	Tangl	1908	52.36	7.09	16.44	0.528	0.871	22.705

(1) Mean of eight analyses on five preparations.
(2) Mean of six analyses on three whitest preparations.
(3) Mean of two. Hot water washing may have removed some S and P.
(4) Mean values for five preparations.
(5) Taken from Tangl, 1908.

From Hammarsten's analytical data Richmond (1901) computed the "probable approximate formula" for casein as separated from cow's milk by Hammarsten's method, $C_{162}H_{258}N_{41}SPO_{52}$, and for the salt separable by the porcelain filter, $C_{162}H_{255}N_{41}SPO_{52}CaNa.I/2(Ca_3P_2O_8)$. The formula given by T. Osborne (1902) is $C_{708}H_{1130}N_{180}S_4P_4O_{224}$, indicating a more condensed molecule. Raudnitz (1903) quotes formulae of the simple protein from Knop, $C_{64}H_{100}N_{16}O_2$ and from Millon- Commaile, $C_{108}H_{97}N_{14}O_{29}$.

PHYSICAL AND CHEMICAL PROPERTIES OF CASEIN

Casein is a white, amorphous powder, practically insoluble in water. It is an acid and as such readily dissolves in solutions of the hydroxides or the carbonates of alkalis or alkaline earths by forming soluble salts. These salt formations have been much investigated. (See Söldner, 1888; Bechamp, 1893; Courant, 1891; de Jager, 1897; Osborne, W. A., 1901-02; Long, 1906a; Robertson, 1906-07, 1908; VanSlyke and Bosworth, 1912, 1913b, 1913c, 1913d; Bosworth and VanSlyke, 1913). L. L. VanSlyke and A. W. Bosworth (VanSlyke and Bosworth, 1912, 1913c; Bosworth, 1913) decide that it has 8 valences toward metals, and that its molecular weight is 8888. The specific rotation of alkali solutions of casein has been investigated by Long (1905,1906a).

Being a protein, casein also forms union with acids, and ion-protein compounds with salt ions. Long (1907b) discusses the combining power toward acids. The alkali or alkaline earth solutions of casein are precipitated by a very little acid, and are soluble in excess of the acid (in most cases). Increase of temperature favors the precipitation by acids. The presence of certain salts is said to favor the solubility of casein and its salts, but sodium chloride, magnesium sulphate and some others "salt out" casein from solution. (See Biedert, 1887; Schröter, 1887; Storch,1897, 1902; Schmidt-Nielsen, 1906; Robertson, 1906-07.)

According to Dakin and Dudley (1913a, 1913b), dilute alkalis acting on casein at low temperatures racemize the casein by tautomeric changes within the protein complex. Such racemized casein, and racemized caseose resulting from it by hydrolysis, were found to escape digestion and absorption when given either *per os* or subcutaneously to a dog.

The most characteristic property of casein is its coagulation with rennet in the presence of lime salts. Hydrolysis by boiling acids, or under the influence of enzymes, cleaves casein as it does other proteins. Buxton and Rake (1911) discuss the various types of coagulation in connection with their study of the flocking out of colloids in general.

COAGULATION BY ACIDS AND BY HEAT

Pure casein salt solutions and fresh milk do not coagulate on boiling, but in the presence of free acid coagulation may take place below the boiling temperature. The coagulum formed in the case of milk includes fat and calcium phosphate. The slight pellicle which coats over milk when it is warmed is of the same composition.

The usually accepted explanation of the precipitation of casein by acids is that the casein is held in solution by chemical union with a base (lime in the case of milk), that added acid removes the base, allowing the insoluble casein to precipitate, and that excess of acid unites with casein forming a compound which is more or less readily soluble. Probably what actually occurs is not quite so simple; it may be rather that there are salts of different proportions of base formed in the presence of different proportions of acid, and that some of these salts are soluble and some are insoluble. L. L. and D. D. VanSlyke (1906, 1907) showed by conductivity methods that in some cases, at least, the taking up of acid is a process of adsorption; while Sammis and Hart (Sammis, 1907a, 1907b; Sammis and Hart, 1909) have shown that the amounts of the different

acids required for coagulation are not chemically equivalent, and that the time required is affected by the presence of other substances as well as by the temperature and the concentration. All of these observations emphasize complication in the process.

The papers of VanSlyke and Hart (1902, 1905a, 1905c) should be mentioned in this connection. Other studies of VanSlyke and Hart consider the reaction with acids particularly in relation to cottage cheese (1904) and to the so-called "mottling" of butter (1905b).

In the coagulation it may be that, in addition to such chemical changes as have been described, there is also concerned a chemico-physical aggregation of molecules as suggested by T. Brailsford Robertson (1908) in the article, "On the Influence of Temperature upon the Solubility of Casein in Alkaline Solutions." In this connection the nature and complexity of casein as a protein should be borne in mind. The protein molecule always shows both acid and basic qualities—is amphoteric—indicating that it yields both hydrogen (H^+) and hydroxyl (OH^-) ions on electrolytic dissociations such as is conceived to take place spontaneously in any water solution. The molecule may be represented by the formula HXOH, in which X represents a carbon nucleus of variable complexity. Any two such molecules may unite, and, with the elimination of water, form a molecule of the type HXXOH, according to the equation:

$$HX(OH+H)XOH=HXXOH+H_2O.$$

Proteins generally are made up by the union of simple bodies of this type.

According to Robertson's conception, in a solution of a protein or its salt the molecules of the protein unite with each other to a certain extent, in this way forming polymers. The reaction is reversible, and the point of equilibrium between the compound and its polymeric modification varies under the influence of whatever condition affects the concentration of the protein ions. Addition of water, or of acid, alkali or salt, or the application of heat has such an effect, and consequently alters the relative number of heavier molecule-complexes. Robertson's experiments give evidence that one of the effects of increase of temperature on a solution of casein is a shifting of the equilibrium in the direction of the higher complexes. He explains coagulation as being a result of these molecular aggregates becoming so large as to assume the properties of matter in mass and to become practically an unstable suspension and then a precipitate.

COAGULATION OF CASEIN BY RENNET

For general discussions see Fuld (1902b) and Kastle and Roberts (1909).

The Enzyme. Coagulation is brought about by an enzyme called "rennin" or "chymosin," which is usually obtained from the water infusion of the fourth stomach of the calf or sheep. As was first noted by Bang (1900c), the corresponding enzyme obtained from the gastric juice of the pig, of man, and of some other animals differs somewhat from chymosin, and hence is designated "parachymosin." It has been shown that this parachymosin action is to be attributed to pepsin, the same enzyme which has the proteolytic action in these juices, and that proteolytic enzymes generally have coagulating power under suitable conditions. Several workers hold also that the distinction between chymosin and parachymosin is apparent, not real, and that chymosin also is identical with pepsin. Many articles have appeared, mainly in Hoppe-Seyler's Zeitschrift für physiologische Chemie, on the two sides of this controversy. For a recent discussion of evidence for the identity, see Van Dam (1912); and for counterargument and evidence, see Rakoczy (1913). Rakoczy interprets his experiments, and harmonizes those of others, by the theory that there is in the stomach of young animals of certain species (notably the calf) an independent coagulating enzyme accompanying the pepsin, though the pepsin also has coagulating action of its own together with its proteolytic action, but this special enzyme is lacking in the adults of the same species and in the young of other species. He notes also that in the very young of some species both enzymes are entirely lacking and coagulation is due only to the acid of the stomach.

Enzymes (or their zymogens) having rennin-like action are found in several organs of the higher animals and in blood (see Edmunds, 1896), and they are said to occur even in invertebrates, and to be widely diffused in the plant world. That of the pancreatic gland has been most studied. (See Roberts, 1879, 1881; Edkins, 1891; Harris and Gow, 1892; Halliburton and Brodie, 1896).

The Coagulum and Conditions for its Formation. Rennet coagulation differs from coagulation by acids, and cannot be looked upon as a simple removal of the base from a caseinate. The presence of soluble calcium salts (or other alkaline earth salts) seems to be essential, and the precipitate formed is not casein or a casein salt, but a salt of a slightly different nucleoalbumin called "paracasein." Many writers, following Halliburton, call this modification produced

by rennin the "casein," and that from which it is derived, "caseinogen." Foster and a few others have used the term "tyrein" for the rennet clot.

A number of investigations have been made concerning the conditions essential or favorable to formation of the coagulum, especially with regard to the effects of the degree of acidity and of conditions affecting the amount of calcium present, either as free soluble salt or bound to the casein. (Hammarsten, 1877; Schaffer, 1887; Söldner, 1888; Arthus and Pagès, 1891; Courant, 1891; Lezé and Hilsont, 1894; de Jager, 1897; Locke, 1897; VanSlyke and Hart, 1902, 1905a, 1905c; VanDam, 1909a; Van Slyke and Bosworth, 1912; Bosworth, 1913; Schryver, 1913.) Soluble salts of calcium, barium and strontium favor or hasten coagulation, while salts of ammonium, sodium and potassium retard or prevent coagulation.

The bulk of the coagulum from milk is a calcium paracaseinate, but it carries down with it calcium phosphate and fat, both of which bodies have been helped to remain in their state of suspension in milk by the presence of the casein salt. Lindet (1912a, 1912b) has concluded that about one-half of the phosphorus contained in the rennet curd is in the form of phosphate of lime (probably tricalcic), the other half being organically combined phosphoric acid.

Hammarsten's Interpretation of the Process of Rennet Coagulation. According to Hammarsten (1877, 1896), whose view has been commonly held, the distinctive effect of the ferment is not precipitation, but is the transformation of casein into paracasein. This is evidenced by the fact that if rennet be allowed to act on solutions free from lime salts no precipitate occurs; but there is an invisible alteration of the casein, for now, even if the ferment be destroyed by boiling the solution, addition of lime salts will cause immediate coagulation. (See also Spiro, 1906.) Hence the process of rennet coagulation is a two-phase process; the first phase is the transformation of casein by rennin, the second is the visible coagulation caused by lime salts.

Furthermore, if the purest casein and the purest rennin were used, Hammarsten always found after coagulation that the filtrate contained very small amounts of a protein. This protein he designated as the "whey protein."

In accordance with these observations, Hammarsten (1911) explains the rennin action "as a cleavage process, in which the chief mass of the casein, sometimes more than 90 percent, is split off as paracasein, a body closely related to casein, and in the presence of sufficient amounts of lime salts the paracasein-lime precipitates out while the proteose-like substance (whey-protein) remains in solution."

By continued action of rennin on paracasein a further transformation has been found in several cases (Petry, 1906; VanHerwerden, 1907; VanDam, 1909b), but perhaps due to a contamination of the rennin with pepsin, or to the identity of these two enzymes. The action which forms paracasein and whey protein takes place in a short time (Hammarsten, 1896; Schmidt-Nielsen, 1906). The composition and solubilities of paracasein have received considerable attention. (See Loevenhart, 1904; Kikkoji, 1909; VanSlyke and Bosworth, 1912.) It is more readily digested by pepsin-hydrochloric acid than is casein (Hösl, 1910).

Duclaux (1884c) and Loevenhart (1904) and others do not accept Hammarsten's theory; but to most workers it seems probable, at least, that the action of the rennin is to cause a cleavage of casein with formation of paracasein. However, the chemical and physical differences observed between casein and paracasein appear to be so slight that Loevenhart and some others think that they are only physical, perhaps differences in the size of the colloid or solution aggregates. Loevenhart conceives of a large part of the work of the rennet (or of the acid, in acid and heat coagulation) as being a freeing of the calcium to make it available for precipitation. Some think that the aggregates of paracasein are larger than those of casein, but there is more evidence of their being smaller, which idea corresponds with the findings of Bosworth, though he looks upon the change as a true cleavage.

Bang's Description of the Precipitation. Bang (1911b) studied the progress of the coagulation process by means of interruptions at definite intervals. His observations confirm the idea that rennin causes the formation of paracasein, and that the calcium salt serves only for the precipitation of the paracasein; the rennin has to do also with the mobilizing of lime salts. According to Bang, before coagulation occurs paracaseins with constantly greater affinity for calcium phosphate are produced. These take up increasing amounts of calcium phosphate, until finally the combination formed can no longer remain in solution.

Bosworth's View of the Rennin Action. By a very recent work of L. L. VanSlyke and A. W. Bosworth (VanSlyke and Bosworth, 1912, 1913a, 1913b, 1913c; Bosworth and VanSlyke, 1913) in which ash-free casein and paracasein were compared as to their elementary composition, and as to the salts they form with bases, and the properties of these salts, it is indicated that the two compounds are alike in percentage composition and in combining equivalent, the paracasein molecule being one half of the casein molecule. Moreover, Bosworth (1913) has shown that, if the rennin cleavage be

carried out under conditions which avoid autohydrolysis, no other protein is formed; also that, if the calcium caseinate present be one containing four equivalents of calcium, the paracaseinate does not precipitate, save in the presence of a soluble calcium salt, while, if the calcium caseinate be one of two equivalents of base, rennin does cause immediate coagulation. Bosworth concludes that the rennin action is a cleavage (probably hydrolytic) of a molecule of caseinate into two molecules of paracaseinate, the coagulation being a secondary effect due to a change in solubilities, dicalcium paracaseinate being soluble in pure water but not in water containing more than a trace of calcium salt, and the monocalcium caseinate being insoluble in water. The alkali paracaseinates, as well as caseinates, are soluble. This explanation seems to promise to harmonize the observations with regard to acidity and the effects of the presence of soluble salts.

The investigations of these authors and of Hart with regard to the changes which the paracasein, the calcium and the phosphorus undergo during the ripening of cheese (VanSlyke and Hart,1902, 1905a, 1905c; VanSlyke and Bosworth, 1907, 1913d; Bosworth, 1907) contributed toward this interpretation.

Mellanby (1912) holds an altogether different idea. He represents the coagulation of milk as due to an absorption of a proteolytic enzyme (rennin is considered to be identical with pepsin) by the casein, and the precipitation of this complex by calcium ions, or other such ions, the calcium being supposed to act by reason of its electric charge without entering into chemical union.

Schryver (1913) has a theory that the action of the enzyme is to free the surface of the complex colloidal molecules from adsorbed compounds which interfere with aggregation.

HYDROLYTIC CLEAVAGE OF CASEIN

Since casein is a protein, it undergoes hydrolysis when boiled with mineral acids or alkalis, or when warmed with the digestive proteolytic enzymes. Under the influence of any of these agents the elements of the water molecule enter into the molecule of the protein, and the protein molecule splits into simpler units. Aside from the phosphoric acid, the nature of the intermediate and final products, as far as known, is the same for casein as for other proteins. The processes are complex and but partially understood.

The latest complete analysis of casein which we have seen is that of T. B. Osborne and H. H. Guest (1911). From their own determinations and from all data previously published they collected a table of the highest values which had been found up to that time

by methods which were considered reliable. It is to be noted that there is still about a third of the molecule unaccounted for, owing to faults in the methods or difficulties in manipulation. We give their table below together with the only other such analyses we have found which are at all extensive. (Abderhalden, 1905; Osborne and Guest, 1911; Abderhalden and Schittenhelm, 1906b; Abderhalden and Langstein, 1910. See also Abderhalden and Funk, 1907, and those referred to in the table.)

HYDROLYTIC CLEAVAGE PRODUCTS OF CASEIN—Percent

Cleavage products	Formulae	Casein from cow's milk		From goat's milk	From human milk
		Table of Abderhalden, 1905	Table of Osborne and Guest, 1911	Analysis by Abderhalden and Schittenhelm, 1906b	Analysis by Abderhalden and Langstein, 1910
Glycocoll	$C_2H_5NO_2$	0.00	0.00	.....	.....
Alanine	$C_3H_7NO_2$	0.9	1.50 [1]	1.5	1.2
Valine	$C_5H_{11}NO_2$	1.0 *	7.20 [1]	.....	1.3
Leucine	$C_6H_{13}NO_2$	10.5	9.35 [2]	7.4	8.8
Proline	$C_5H_9NO_2$	3.1 †	6.70 [3]	4.62	2.85
Phenylalanine	$C_9H_{11}NO_2$	3.2	3.20 [4]	2.75	2.8
Glutaminic acid	$C_5H_9NO_4$	10.7	15.55 [1]	11.25	10.95
Aspartic acid	$C_4H_7NO_4$	1.2	1.39 [1]	1.1	1.0
Cystine	$C_6H_{12}O_4N_2S_2$	0.065 [5]	?	.....	.....
Serine	$C_3H_7NO_3$	0.23 [6]	0.50 [6]	.....	.....
Tyrosine	$C_9H_{11}NO_3$	4.5	4.50 [7]	4.95	4.58
Oxyproline	$C_5H_9NO_3$	0.25§ [8]	0.23 [8]	.....	.....
Histidine	$C_6H_9N_3O_2$	2.59 [9]	2.50 [10]	.....	.....
Arginine	$C_6H_{14}N_4O_2$	4.84 [9]	3.81 [10]	.....	.....
Lysine	$C_6H_{14}N_2O_2$	5.80 [9]	5.95 [10]	.....	.....
Tryptophane	$C_{11}H_{12}N_2O_2$	1.5	1.50 [4]	.....	.....
Diaminotrioxydodecanic acid‡	$C_{12}H_{26}N_2O_5$	0.75 [11]	0.75 [11]	Present	.....
Ammonia	NH_3	.....	1.61 [12]	.....	.....
Sulphur	S	.....	0.76 [13]	.....	.....
Phosphorus	P	.....	0.85 [13]	.....	.....
Sum	.....	51.13	67.85	.....	.....

(*) Amino-valerianic acid. (†) Pyrrolidine-carboxylic acid. (§) Oxy-α-pyrrolidine-carboxylic acid. (‡) Sometimes called "caseinic acid."

Authors to whom credit is given: (1) Osborne and Guest. (2) Levene and VanSlyke, original has "leucine+isoleucine." (3) VanSlyke. (4) Abderhalden. (5) K. A. H. Mörner. (6) Fischer, original has 0.5 percent. (7) Reach. (8) Fischer, original has 0.23 percent. (9) E. Hart. (10) Osborne, Leavenworth and Brautlecht. (11) Fischer and Abderhalden. (12) Osborne and Harris. (13) Hammarsten.

Folin and Denis (1912) have recently reported the determination of tyrosine by a new colorimetric method. They find 6.5 percent in casein. E. Fischer and Abderhalden (1903) by enzyme digestions found α-pyrrolidine carbonic acid.

With regard to the relation of phosphorus to the casein molecule, Osborne and Guest say in their discussion: "The presence of phosphorus in casein raises the question as to whether it is a constituent of the protein molecule or of some non-protein group united with a protein group as is a haematin with globin in haemoglobin, or nucleic acid with protein in the nucleins. Such data as are available indicate that the union is other than a salt-like combination of a phosphorus-containing acid with a protein base." Calculations from the amount of the casein and of its nitrogen unaccounted for by the above analyses "give no evidence that casein differs in constitution to any marked degree from other proteins which contain no phosphorus. It might be supposed that the phosphorus of casein was a part of some organic radical.....If this is, in fact, so the organic radical must be one which contains nitrogen in approximately the same proportion as the mono-amino-acids."

DIFFERENCES IN THE CASEIN FROM DIFFERENT KINDS OF MILK

Consistency of the Coagulum. There is a marked difference in the appearance and the digestibility of the coagulum formed by acids or rennet in cow's milk and human milk. The milk of the mare and the ass (Langgaard, 1875; Ellenberger, 1899; Storch, 1902; Zaitschek, 1904; von Szontagh, 1905) are said to resemble human milk in this respect and, according to Arthus and Pagès (1891), the milk of the dog also belongs in this class. The cow's milk gives a much tougher and more compact coagulum, in coarser flakes, than the small, jelly-like flakes from human milk. This difference, however, may not be due to any chemical difference in the casein itself. Certain observations indicate that it might be due to the greater proportionate amount of fat in the human milk (Hempel, 1894), or of salts in cow's milk (Dogiel, 1885), or to the acidity of cow's milk (Courant, 1891). Soxhlet (1893) says that dilution of cow's milk reduces the size of the flakes. Biedert and Schröter (Biedert, 1887; Schröter, 1887) notice great differences in the amount precipitable with $MgSO_4$. Ass's milk is not easily coagulated by acids and its casein not easily salted out by salts (Storch, 1902), and the coagulum is fine.

Completeness of Peptic Digestion. Early investigators report that peptic digestion of cow's casein leaves an insoluble, undigested nuclein (pseudonuclein) but casein from human milk does not (von Szontagh, 1892, 1894; Willdenow, 1893; von Moraczewski, 1895a; Alexander, 1898); but later work seems to prove that this difference is merely one of the ease of digestion of the two pseudonucleins. (Wróblewski, 1894a, 1894b; Sebelien, 1894, 1895; Salkowski, 1893a, 1893b, 1896a; Salkowski and Hahn, 1894-5; Kobrak,

1900; Rotondi, 1902). Salkowski says that the casein will be completely digested if the ratio between casein and digesting liquid is 1:500 and the casein has previously been dissolved so that the influence of hard, dried particles of casein is excluded. About 1 percent remains undissolved if the ratio of casein to solvent is 1:250. Zaitschek and von Szontagh (Zaitschek, 1904; von Szontagh, 1905) found woman's, ass's and mare's milk completely digested in 72 hours at 38°C., while only 8, 14 and 15 percent, respectively, of the casein of cow's, buffalo's and goat's milk is rendered soluble under the same conditions. Long (1906a, 1907a) finds the caseins of goat's and cow's milk much alike, but the former has a somewhat higher equivalent weight than the latter, and it is more slowly acted on by pepsin-hydrochloric acid, and leaves more pseudonuclein.

Elementary Composition. By reference to the table on p. 35 it will be seen that there is not much difference in the elementary composition of caseins from various sources except as to the phosphorus content. Probably the analyses of Langstein and Edelstein (1910) are the best we have on human casein. Then, as compared with about 0.85 percent phosphorus in cow's casein, we find only about 0.24 percent in human casein and as high as 1.04 percent in ass's casein.

Products of Complete Hydrolysis. The analyses of Abderhalden and his associates (see p. 42) show, so far as they go, no marked differences between the cleavage products of the caseins from cow's, goat's and woman's milk, considering the lack of close agreement of all such determinations. On the other hand, they by no means exclude the possibility of significant differences of this kind, as accounting for the variations in elementary composition and in chemical behavior.

Other Comparisons. In the other ways in which caseins have been compared—as to solubilities, reactions with chemicals, repeated solution and reprecipitation, pancreatic digestion and nutritive value—there seems to be enough similarity observed to indicate that all the caseins are alike in general nature, but unlike in some chemical respects which are not yet determined. J. Bauer and St. Engel (1911) concluded that the caseins from cow and human milk are alike.

THE PHOSPHORUS OF CASEIN

What is to be said as to the form in which phosphorus is present in casein? The quotation from Osborne and Guest shows that practically nothing is known as to the nature of that within the protein itself, not even whether it be present as a phosphoric acid radical

or as a nitrogenous, organic complex. Aside from the phosphorus within the protein, casein is also practically always intimately associated with calcium phosphate.

Perhaps the synthetic work of Neuberg and Pollak (1910b, 1910d) throws some light on the nature of the combination of phosphorus in the phosphoprotein molecule, as well as that in the nuclein molecule. At least, they have succeeded in bringing about a union of simple proteins (lactalbumin and blood globulin) with the phosphorus of phosphorus oxychloride. A substance obtained in this way had an elementary composition much like that of casein (but with somewhat higher phosphorus content) and yielded to pancreatic and peptic digestion in just about the same way as casein. The authors looked upon this compound as a substituted phosphaminic acid. With the simple amino acids or their esters they were able also to cause organic union of the phosphorus, but the organic phosphorus compounds were not isolated.

OTHER PHOSPHOPROTEINS

OVOVITELLIN

Ovovitellin is the lecithalbumin found in the yolk of hen's eggs. It is a combination of protein with lecithin, the lecithin not being removable by ether. According to T. B. Osborne and Campbell (1900b) the body which has been studied under this name is a mixture of various vitellin-lecithin combinations, containing from 15 to 30 percent of lecithin. The protein, moreover, when freed from lecithin still contains phosphorus. Osborne and Campbell give the composition of this protein (which they call "nucleovitellin"): C=51.24; H=7.16; N=16.38; S=1.04; P=0.94; O=23.24 percent. Hammarsten (1911) tells us that Gross (Zur Kenntniss des Ovovitellins, Inaug. Diss., Strassburg, 1899) gave the analysis of vitellin prepared by $(NH_4)_2SO_4$ precipitation as follows: C=48.01; H=6.35; N=14.91—16.97; P=0.32—0.35; S=0.88 percent; and we have from T. B. Osborne (1902) the formula $C_{671}H_{1112}N_{182}S_5P_4O_{227}$, with 0.82 percent P.

Plimmer (1908) found 0.65-1.14 percent P, with a mean of 0.99 percent in five preparations examined. Plimmer found with the vitellin in egg-yolk another protein having a lower phosphorus content (0.10-0.85 percent P, with a mean of 0.35 percent in five preparations), which he suggests may be vitellin without its phosphorus-containing portions. He gave the new substance the name "livetin."

Abderhalden and Hunter (1906) and T. B. Osborne and D. B. Jones (1909) report the following cleavage products:

CLEAVAGE PROUCTS OF VITELLIN OF HEN'S EGG—Percent

Acid	Abderhalden and Hunter (1906)	Osborne and Jones (1909)
Glycocoll	1.1	0 00
Alanine	Present	0 75
Amino-valerianic acid (Valine)	2 4	1 87
Leucine	11 0	9 87
Aspartic acid	0 5	2 13
Glutaminic acid	12 2	12 95
Phenylalanine	2 8	2 54
Proline	3 3	4 18
Serine	?	?
Tyrosine	1 6	3 37
Cystine	Not determined	Not determined
Histidine	"	1 90
Arginine	"	7 46
Lysine	"	4 81
Ammonia	"	1 25
Tryptophane	"	Present
Phosphorus	"	0.94
Total	Not complete	54.02

Folin and Denis (1912) found in ovovitellin 5.2 percent tyrosin.

The study of Osborne and Campbell already cited includes examination of the paranuclein resulting from peptic digestion. By repeated digestions they obtained substances containing 3.29, 2.52 and 4.19 percent P. They interpret their analyses as showing that this paranuclein and the paranucleoprotein from which it was derived "are both compounds of one and the same proteid body [which is free from phosphorus, and which these authors call "vitelline"] with a phosphoric acid, possibly H_3PO_4, $H_8P_2O_9$, or some simple organo-phosphoric acid." For the paranucleic acid prepared by Levene and Alsberg (1901) the phosphorus content is given as 9.88 percent P.

Bunge (1885a) made a study of the paranuclein derived from peptic digestion of the egg-yolk as a whole. In this body he found 5.19 percent P, Hugounenq and Morel (1905a, 1905b) later finding 8.7 per cent P. This body Bunge looked upon as that from which haemoglobin is made for the young organism, and he gave it the name "haematogen." The significance of the iron content is emphasized.

Finally, it is evident that much more study may well be given to the constitution and metabolic possibilities of ovovitellin, which is so significant for the development of the young bird, and important as a food for man. Phosphorus is present in a lecithin portion

and in a protein portion, and probably the two are chemically combined. In the lecithin fraction it is glycerylphosphate, and in the protein fraction some undetermined radical, very likely a simple phosphoric acid or a phospho-organic acid.

ICHTHULIN

The compound in the eggs of fish corresponding to the ovovitellin of hen's eggs has been given the name "ichthulin." The two were early studied together and their similarities in chemical nature as well as biological significance were pointed out. (See Gobley 1850a; Valenciennes and Frémy, 1854; Diaconow, 1867a; G. Walter, 1891; Levene, 1901a; Hammarsten, 1905a; Plimmer and Scott, 1908; Gobley quotes other authors as far back as 1817.) Such a body has been isolated and studied from the eggs of carp, sturgeon, cod and perch. Levene (1901a) formed the paranuclein by peptic digestion, and reports the analysis of the paranucleic acid, which corresponds with that of the product from ovovitellin. This acid (not entirely free from protein) showed 10.34 percent P. We give below Levene's table of the analyses of ichthulin made by different workers, and add values taken from Hammarsten's (1905a) later report.

ELEMENTARY ANALYSIS OF ICHTHULIN FROM FISH EGGS—Percent

Author	Kind of fish	C	H	N	S	P	Fe	O
Frémy	Salmon	52.5–53.3	8.82	15.2	1.00	0.6	. ..	22.7
Gobley	Carp	52.6	7.74	15.5	0.90	0.37	....	23.24
Walter	Carp	53.52	7.6	15.63	0.41	0.43	0.10	22.19
Levene	Cod	52.44	7.45	15.96	0.92	0.65	....	22.58
Hammarsten	Perch	.....	....	14.81	1.111	0.743	....	.....

OTHER PHOSPHOPROTEINS OF ANIMAL ORIGIN

Hammarsten (1885b) reports obtaining a nucleoalbumin from the albuminous gland of a snail. This body is spoken of as "helicoproteid from the name of the snail (Helix pomatia). Liebermann (1891a, 1891b, 1893a, 1893b) isolated what he called lecithalbumins from the mucous membrane of the stomach (hog), from kidney (sheep), liver (lamb), lungs and spleen. He called especial attention to the observations that these substances are strongly acid, and readily form union with alkalis or other basic bodies, that they are rendered still more acid by CO_2; then by soda solutions are

rendered strongly alkaline, and afterward can again be made acid by CO_2. He suggests that in the stomach walls they may thus serve in the production of hydrochloric acid from sodium chloride by taking up the sodium temporarily and gradually giving it up to the CO_2 of the blood. He also found that the alkaline solutions of Na_2HPO_4, or of sodium urate carrying a slight excess of soda, when passed through these lecithalbumins as a filter, show a strongly acid filtrate, and leave a strongly alkaline residue on the filter. This he suggests may indicate the process by which an acid urine may result in the kidney from filtration from alkaline blood.

Lönnberg (1890) looking for mucin in the cortical and medullary substance of the kidney and the mucous membrane of the urinary bladder, decided that the bodies he isolated were not true mucins, but were nucleoalbumins. Malengreau (1900) found two nucleoalbumins in the thymus.

Plimmer and Kaja (1909); also Plimmer and Scott (1908) report phosphoproteins in the pancreas and pancreatic juice of the dog, in the salivary glands of sheep and in the eggs in the ovary of the frog. They did not find them in the testes of the ox or of codfish, nor in thymus.

PHOSPHOPROTEINS OF VEGETABLE ORIGIN

From time to time proteins containing phosphorus have been isolated from plant bodies, and some of these so closely resemble the animal phosphoproteins in their properties that Liebig gave them the name of vegetable casein; this name, however, was generally given up when, later, Weyl showed that none of the substances most resembling casein are present in the natural bodies, but that there are there such as may be called plant vitellins—phyto-vitellins. All of the investigations of these compounds are thrown somewhat in doubt because of the presence of considerable amounts of salts such as potassium, calcium, or magnesium phosphates, or of alkalis in combination with organic acids, which are very difficult of removal. Hammarsten (1911, p. 105) says: "It is not clear whether the phosphorized plant proteids contain their phosphorus as impurities or whether they are the same as the animal phosphoproteins."

The vegetable vitellins that have been most thoroughly investigated are, according to Gustav Mann, (Chemistry of the Proteids, 1906 pp. 374, 375; 23 references on this subject), the gluten-casein of wheat; similar substances from rye, maize, spelt and barley; legumins from peas, vetches, beans, lentils, etc. (T. B. Osborne says that these are globulins); conglutins (so named by Ritthausen) of lupines, almonds, nuts, etc. Several of these have been analyzed by Ritthausen and by Osborne.

We have not found report of any recent work on any of the compounds of this group.

PHOSPHOCARNIC ACID

Phosphocarnic acid is a complex phospho-nitrogenous compound the nature of which seems never to have been fully determined, the substance never having been isolated free, but only in its iron compound, carniferrine, or mixed with decomposition products. It was first described by Siegfried in 1894 (see Siegfried 1894, 1895, 1896) who obtained it at first from prepared meat extracts and later directly from muscle. It is perhaps the most important organic phosphorus compound among the meat extractives. The properties make it well fitted to serve as a carrier of phosphoric acid, iron, lime and magnesia in the body fluids, since it readily unites with the basic elements and forms with them compounds soluble in either neutral, weakly acid or weakly alkaline solutions. It probably has a similar significance in milk, of which also it is a constant constituent.

The cleavage products which Siegfried obtained from phosphocarnic acid are carnic acid (which seems to be identical with, or closely related to, the antipeptone of Kühne), phosphoric acid, carbon dioxide, a carbohydrate group which reduces Fehling's solution, succinic acid and paralactic acid. (See also T. R. Krüger, 1896.)

Since carnic acid is a peptone, phosphocarnic acid differs from nucleins primarily in that on hydrolytic cleavage it yields a peptone direct instead of a protein. For such compounds Siegfried proposed the name "nucleon," and he designated phosphocarnic acid as muscle-nucleon."

The nucleon obtained from milk showed nearly the same composition as that from muscle, but yielded decomposition products of slightly different properties; the lactic acid obtained was not paralactic but was fermentation lactic acid, and in place of carnic acid there was obtained a modification designated as orylic acid.

T. R. Krüger (1899) states that milk nucleon is not precipitated by ammonium sulphate, while the muscle nucleon is so precipitated, and that such precipitation alters the proportion of N to P. Siegfried (1899) pointed out at the same time that the precipitates which he and others were obtaining from muscle were not uniform in the ratio of nitrogen to phosphorus, which might be due to the existence in muscle of nucleons of different composition. That would not be the only possible explanation of this inconsistency, however, for it is possible that differences in the conditions of precipitation

brought down a mixture of substances, or even caused some slight decomposition of the nucleon. In Siegfried's analyses of carniferrine from muscle reported in 1896 the nitrogen content ranged from 5.45 to 6.03 percent, the mean of six determinations being 5.65 percent. The phosphorus content found in four cases ranged from 1.84 to 2.59 percent (P), the mean being 2.12 percent. Using the mean value for nitrogen, and relating it to the lowest and highest values for phosphorus, gives the ratio N:P as 3.07 and 2.18 respectively. The ratio N:P found at this time in a preparation from muscle of a new born calf was as 1:1, and Krüger had found a ratio of 1:1 during his work with muscle from a steer. Macleod (1899), in the same laboratory, had precipitated carniferrine from the extracts of muscle from a number of dogs, and had found that they varied in this respect. The analyses he gives of nine such extracts show these values for N:P,—4.3, 1.6, 1.8, 1.5, 1.7, 1.5, 1.3, 2.0, 3.7.

This all gives sufficient evidence that we have not a uniform product, and that if phosphocarnic acid is a chemical unit it undergoes decomposition in the processes used in isolation.

The animal substances in which phosphocarnic acid has been found (or, rather, from the water extracts of which its iron complex has been precipitated after removal of proteins and phosphates) are as follows:

By Siegfried (1896): Liebig's and Kemmerich's meat extract, beef muscle, dog's liver and heart, and cow's milk.

By Balke and Ide (1896): Kemmerich's meat extract, the heart, liver and kidney of horse and of dog.

By Wittmaack (1897): The milk of cow, woman and goat.

By Panella: The striated muscle fibre of dogs and rabbits (Panella, 1902a, 1903b); brain of dog, rabbit and calf (Ditto, 1902b, 1903a); blood of dog, rabbit and calf (Ditto, 1902c, 1903c); both white and red muscle of rabbit (Ditto, 1903e, 1903f); testicular substance of ass and horse (Ditto, 1903d); both white and gray matter of brain (Ditto, 1903g, 1903h); testicular substance of horse (Ditto, 1903i, 1904a); non-striated muscle, in larger amount than in striated (Ditto, 1904b); spleen of cattle, horses, sheep, swine and dogs (Ditto, 1904c); the amount in the brain of the dog falls off during fast (Ditto, 1906a).

In 1906 Panella (1906b) published a paper which seems to throw doubt on the numerical data of previous work by showing that the values found for muscle are too high if less than 20 gm. of substance are taken as the sample. Using 50gm. or more as sample

yielded nearly constant results of about 0.01 percent nucleon in fresh muscle, or 0.02–0.03 percent in dry. These values are much lower than those which were earlier reported.

PHYTIN

Introduction. The literature of the chemical study of phytin has recently been reviewed by A. R. Rose (1912b) with especial reference to its significance in plant economy. This review is published in the Biochemical Bulletin, and is the most complete discussion to which we can refer the reader.

Phytin is the name generally applied to the alkali and alkaline earth salts of an organic phosphoric acid which is found extensively in the vegetable world, and which by most investigators is supposed to contain inosite combined in some way with phosphoric acid. It appears now probable that the natural products are not all identical, and distinction must be made between the salts of phytic acid and of other phyto-phosphoric acids. Rose calls the acid "inosite-phosphoric acid."

Discovery. Rose tells us that the aleurone grains, in which this compound is found in seeds, were first discovered microscopically by Hartig in 1854, and that the particular P-bearing spheroidal bodies in these grains were isolated by Pfeffer in 1872, and named by him "globoid." Chemical study began with Palladin in 1893, who obtained it from *Senapis niger*. He showed the compound to be rich in phosphorus, and to contain magnesium and calcium but no nitrogen; also that it was non-reducing and yielded no reducing substance on acid hydrolysis. Palladin's work was followed up by Schulze and Winterstein (1896) and Winterstein (1897) who identified the body with the globoid of Pfeffer. The name "inosite-phosphoric acid" was proposed by these investigators in accordance with their finding that the magnesium salt on being digested for 30 hours with conc. hydrochloric acid at 130–140° yielded inosite and phosphoric acid. Posternak studied the substance extensively (Posternak, 1900, 1903a, 1903b, 1903c, 1903d, 1905; and Bull. Soc. chim. 33 (1904), 116). He considered that the inosite was not preëxistent in the molecule, but that the compound was an anhydro-oxymethylene-diphosphoric acid, and he gave it the name "phytin," which has been retained.

Occurrence. Phytin is found most frequently in the aleurone of seeds or in other parts of plants which serve for storage, as some roots and tubers. Of investigations as to the amount of phosphorus present in this form we mention Schulze and Winterstein (1896),

Posternak (1903a, 1903b), Hart and Andrews (1903), Patten and Hart (1904), Suzuki and Yoshimura (1907), Suzuki, Yoshimura and Takaishi (1907), Vorbrodt (1910), Rising (1910), Hart and Tottingham (1910), and Bernardini (1912).

ANALYTICAL DATA ON THE OCCURRENCE OF ORGANIC PHOSPHATE PHOSPHORUS, "PHYTIN"—Percent

Substance analyzed	Author	Phosphorus in the form of organic phosphate	Fraction of total phosphorus in this form
Black mustard (*Sinapis nigra*) (1)	Schulze, Winterstein	0.33	....
Red fir	Posternak	0.60	91.46
Spruce seed (*Picea excelsa*) (2)	Vorbrodt	0.15	21.65
Pine seed (*Pinus cembra*) (2)	Vorbrodt	0.07	14.39
Hempseed (cortex removed)	Posternak	1.33	91.44
Hempseed (*Cannabis sativa*) (2)	Vorbrodt	0.11	15.00
Sunflower seed (cortex removed)	Posternak	0.72	86.26
Pea	Posternak	0.26	70.80
Pea, yellow	Rising	0.11	19.00
White kidney bean	Posternak	0.42	81.60
Bean, brown	Rising	0.29	52.00
Lentils	Posternak	0.25	82.60
Lentils (*Lens esculenta*) (2)	Vorbrodt	0.03	9.29
Windsor bean (*Vicia faba minor*) (2)	Vorbrodt	0.02	4.39
Wheat bran	Patten, Hart	0.92	68.10
Wheat bran (3)	Suzuki, Yoshimura	0.58	52.00
Wheat grain (4)	Suzuki, Yoshimura, Takaishi	....	55.50
Wheat grain (*Triticum sativum*) (2)	Vorbrodt	0.136	29.90
Graham flour	Rising	0.08	29.00
Rice bran (3)	Suzuki, Yoshimura	1.68	74.17
Rice seed (4)	Suzuki, Yoshimura, Takaishi	....	41.64
Rice flour	Rising	0.11	69.00
Rice, seed (5)	Bernardini	0.436	45.90
Rice embryo (5)	Bernardini	5.14	82.90
Barley bran (*Hordeum vulgare*) (3)	Suzuki, Yoshimura	0.24	44.00
Barley, grain (4)	Suzuki, Yoshimura, Takaishi	....	56.55
Barley, grain (6) (5)	Hart, Tottingham	0.19	38.00
Barley bran (6) (5)	Hart, Tottingham	0.15	68.20
Barley grain minus bran (6) (5)	Hart, Tottingham	0.17	29.80
Barley, grain (*Hordeum distich.*) (2)	Vorbrodt	0.17	36.40
Barley, grain (*Hordeum distich.*) (2)	Vorbrodt	0.12	34.30
Rye flour	Rising	0.09	25.00
Rye, grain (*Secale cereale*) (2)	Vorbrodt	0.12	28.90
Millet (*Panicum frumentaceum*) (3)	Suzuki, Yoshimura	0.34	44.97
Sesame seeds (*Sesamum indicum*) (3)	Suzuki, Yoshimura	0.13	16.24
Castor bean, seed (*Ricinus communis*) (3)	Suzuki, Yoshimura	0.11	41.61
Rape seed (*Brassica napus oleifera*) (2)	Vorbrodt	0.20	38.05
Oil cake of rape (*Brassica napus*) (3)	Suzuki, Yoshimura	0.53	44.46
Rape seed (*Brassica napus*) (4)	Suzuki, Yoshimura, Takaishi	....	62.11
Radish root juice (7)	Suzuki, Yoshimura	....	15.13
Turnip root juice (7)	Suzuki, Yoshimura	....	15.06
Apple, juice (7)	Suzuki, Yoshimura	....	48.14
Pear, juice (7)	Suzuki, Yoshimura	....	46.15
Corn, grain (4) (5)	Hart, Tottingham	0.13	44.80
Corn, bran (4) (5)	Hart, Tottingham	0.00	0.00
Corn, germ (4) (5)	Hart, Tottingham	0.13	34.20
Corn, endosperm (4) (5)	Hart, Tottingham	0.15	35.70
Corn, grain (*Zea mays*) (2)	Vorbrodt	0.17	48.90
Oat, grain (4) (5)	Hart, Tottingham	0.18	43.90
Oat, hull (4) (5)	Hart, Tottingham	0.09	21.90
Oat, grain minus hull (4) (5)	Hart, Tottingham	0.22	53.70

(1) Computed. Percent of fat-free seeds. NaCl extract, precipitated hot.
(2) Organic phosphorus soluble in 1.0 percent acetic acid; computed from P_2O_5 by compiler.
(3) Percent of dry substance obtained by absolute alcohol precipitation from 0.2 percent HCl extract.
(4) Organic phosphorus soluble in 0.2 percent HCl.
(5) Percent of total computed by compiler.
(6) Phosphorus soluble in 0.2 percent HCl (considering that the inorganic fraction of this is small enough to be ignored).
(7) Total organic phosphorus of expressed juice; grams per 100 c.c.

To quote freely from Posternak (1903a):

Phytin is stored as reserve material in all grains, tubers, rhizomes and bulbs, where it is destined for the development of the embryo. Other bodies from which it has been extracted besides those reported in this paper are—rape, lupine, wheat, corn, potatoes, dahlia bulbs, carrots and even onions. In the grains, where there is very little mineral phosphate, it forms at least 70-90 percent of the total phosphorus.

Anderson (1912b) was unable to find in wheat bran any of the characteristic salts of phytic acid.

The purified barium salts of the compounds obtained corresponded to the formulae: $C_{25}H_{55}O_{54}P_9Ba_5$ and $C_{20}H_{45}O_{49}P_9Ba_5$. The only acid that could be isolated was $C_{20}H_{55}O_{49}P_9$, and all of the barium salts obtained could be changed into salts of this acid by processes which liberate reducing substances. Hence it was concluded that this acid is the only organic-phosphoric acid present, and that wheat bran does not contain phytin.

Rather (1912, 1913a, 1913b) has investigated a corresponding compound obtained from cottonseed meal. It was his conclusion that this and the wheat bran compound are identical, and that the free acid from both is represented by the formula $C_{12}H_{41}P_9O_{42}$. Anderson (1914a), however, thinks that Rather's silver salt preparations are not chemically pure, and from his own investigations (1912c, 1914a) believes that the organic phosphoric acid in cottonseed meal must be inosite hexaphosphoric acid, $C_6H_{18}O_{24}P_6$, or some multiple of the same. Anderson gives the same formula for compounds obtainable from oats (1914b), from corn (1914c), and, finally, from commercial phytin (1914d).

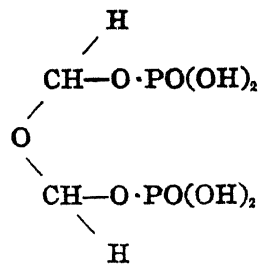
Salts of Phytic Acid. Phytic acid forms neutral salts, acid salts, double salts and acid double salts of the alkalis, alkaline earths and heavy metals. The solubility of these salts decreases in the order above named. The magnesium compounds are more soluble than the calcium, and the calcium more soluble than the barium or strontium. They are all more soluble in cold than in hot water, and heating often precipitates them. Several such salts have been isolated from plant bodies; and Anderson (1911) has added largely to the number by artificial production. Elementary analysis of these salts throws light on the basicity of the acid and the relative number of C and P atoms in the molecule. Rose gives us a table compiled from the various elementary analyses reported in the literature. Rose's conclusion is that the relative number of atoms in the molecule corresponds with the ratio 6C:6P; and—"It seems

probable that the molecular weight when accurately determined will be reported as 714 or will differ from this by the molecular weight of three molecules of water. The molecule seems to contain twelve hydrogen atoms readily separated in ionization, six of which are exceedingly reactive; the remaining hydrogen atoms gradually diminish in activity by twos, the last four being slow to enter into an exchange with bases. The more readily formed salts are therefore those corresponding to an octavalent acid and the other common ones are in six and tenvalent combinations."

Synthesis of Phytic Acid. Anderson speaks of a paper by Contardi, which we have not seen (Atti R. Accad. dei Lincei, Roma [5] 19 [1] 23), in which the author reports having prepared the hexa-phosphoric acid ester of inosite by heating inosite in an excess of phosphoric acid in a stream of carbon dioxide at 160–165°C. The free ester obtained from this preparation was said to be identical with phytic acid. Carré, however, (Bull. Soc. chim. de France [4] 9, 195) repeating these experiments, found that the products described by Contardi were merely mixtures of free phosphoric acid with the alcohol, together with their decomposition products mixed with monobarium phosphate. Anderson has made repeated efforts to synthesize phytic acid, without accomplishing it; nor was he able to synthesize a hexa-phosphoric acid ester of inosite. A tetra-orthophosphoric acid ester, a di-pyrophosphoric acid ester of inosite and a di-inosite tri-pyrophosphoric acid ester were obtained in pure form, and analyzed. (Anderson, 1912a.) Of them Anderson says: "These compounds are in physical and chemical properties very similar to phytic acid. They form analogous acid salts which in appearance and solubility seem almost identical with salts of phytic acid. Whether esters, such as above, are found in nature is at present unknown. It is, however, not impossible that a part of the organically bound phosphorus existing in plants may be present in such, or similar forms."

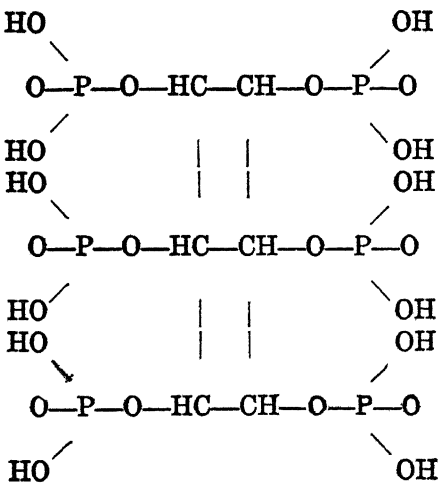
Constitution. Winterstein (1897, 1908), repeatedly obtaining a cleavage of the compound into inosite and phosphoric acid, believed it to be a conjugated inosite-phosphoric acid. Posternak (1903a, 1903d), however, was of the opinion that, although inosite is obtained in such cleavage, the grouping present in the phytin is that of a simpler compound, that of the alcoholic isomer of formaldehyde, CH·OH, and that when this is set free from the acid polymerization occurs, forming the inosite by union of six such groups. He interpreted phytin as being the first product in the organization

of inorganic phosphorus taking place under the influence of chlorophyll in direct sunlight. He called it anhydro-oxymethylene-diphosphoric acid and proposed the empirical formula, $C_2H_8P_2O_9$, and the structure indicated by the following:

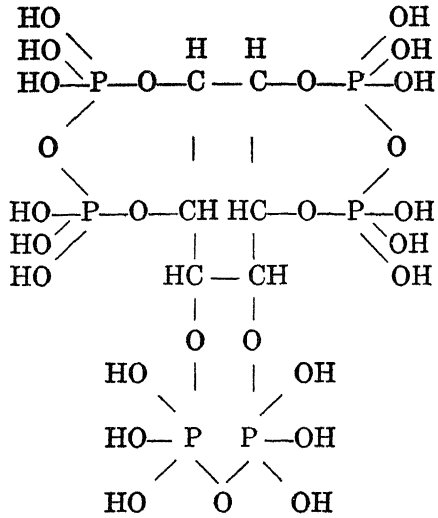


The analyses of Patten and Hart (1904) were said to support this formula.

Suzuki, Yoshimura and Takaishi (1907), because of enzymatic splitting off of inosite, decided that inosite was originally present in the phytin, and that the substance must be inosite hexaphosphoric acid. They constructed the following formula to represent their view.



The discovery by Neuberg (1908) that both inosite and phytin yield furfurol when distilled with phosphorus pentoxide and phosphoric acid, respectively, led him to believe that the inosite ring exists already formed in the phytin, and he suggested the following structural formula:



Levene, (1909a) (to quote from Rose) "working with a preparation from hempseed, was led to believe that the 'phytin' of this grain contained in its molecule phosphate, inosite and a carbohydrate of the pentose group. His work was criticized by Neuberg (1909), who claimed that there were impurities in the preparation. In view of the known intimate association of the phytin with protein and carbohydrate in the aleurone grain, and the possible occurrence of a chemical combination of both phyto-phosphate and carbohydrate with protein, it is conceivable that Levene had a product holding pentose as an integral part and not as an impurity, though in view of all the available evidence Neuberg's criticism seems at the present time somewhat justifiable."

Starkenstein (1910), who thinks that inosite bears some definite relation to the phenomena of growth of animals as well as of plants, believes that the acid to which phytin corresponds is not a simple ester but a complex pyro-phosphoric acid compound, and that the acid salts usually resulting from reaction with divalent metals are to be explained by the union of the divalent atoms with hydroxyls of adjacent phosphoric-acid residues. His interpretation would give the ratios of C:P:OH as 6:6:12, which is supported by most of the analyses. Titration with uranium acetate shows only one half of the true phosphoric acid value, because only one half of the free hydrogens are readily reactive.

The analyses of Levene, Vorbrodt (1910) and Rising (1910) do not support any of these formulae as to the relative amounts of carbon and phosphorus; and we understand that those of Plimmer and Page do not (Chem. Abs.).

Anderson (1914d) has succeeded in obtaining from commercial phytin a crystallizable barium salt, and the acid from the same, analysis of which corresponds with the formula $C_2H_6O_8P_2$ or $C_6H_{18}O_{24}P_6$. No direct evidence has been gained as to the molecular magnitude, but the second formula is thought to be the more probable. This differs from Neuberg's formula for phytic acid by three molecules of water, and is identical with inosite hexaphosphate. Anderson, therefore, believes the phytic acid to be either inosite hexaphosphate or an isomer of the same. He finds, as did Starkenstein, that only one half of the acid hydroxyls are particularly reactive. Both the salts and the free acid when kept at ordinary temperatures decompose slowly, with liberation of inorganic phosphate, the acid decomposing much faster than the salt. Inosite was not found among the products of this spontaneous decomposition.

Possible relations between phytin and lecithin (phosphatids) on the one hand and nucleic acids on the other have been pointed out by Iljin (1906), Parrozzani (1909) and Rising (1910).

Phytin-Splitting Enzyme. Suzuki, Yoshimura and Takaishi (1907) isolated an enzyme from rice and wheat bran which splits phytin into phosphoric acid and inosite, and which is probably widespread in the plant world. They named the new enzyme "phytase."

A part of Vorbrodt's (1910) study was with regard to enzymatic decomposition of the organic phosphorus compounds of barley and corn. He concluded that:

"1. The organic phosphorus compounds of barley and corn grains, both those soluble in 1% acetic acid and those insoluble, can be decomposed under the influence of enzymes, in which process mineral phosphoric acid is split off.

"3. Temperature exerts a decided influence on the progress of the decomposition of the organic phosphorus compounds; a little above 0° there is no decomposition of the soluble organic phosphorus compounds of barley, the optimum is about 28°C., above 48° the progress of decomposition is very slow.

"4. The enzymes which split the organic phosphorus compounds are already present in the barley grain, but in the corn grain the amount is very insignificant; they develop in large amount during germination, when they are present more abundantly in the germ and the scutellum than in the rest of the seed.

McCollum and Hart (1908) found evidence of such a phytin-splitting enzyme in the liver and the blood of the calf, but not in the muscle or kidney.

Jegorow (1912) doubts the existence of phytase, since under the conditions of the work by Suzuki phosphoric acid splits off without the enzyme preparation. He finds phytin quite unstable. Inosite and phosphoric acid result from boiling with water.

PHOSPHATIDS

INTRODUCTION

Our present knowledge of the phosphatids has been attained largely through the systematic study of the composition of the brain. Of these studies the most significant as supplying a basis for the classification of phosphatids (originating the name "phosphatid") was that of Ludwig W. Thudichum (1901). Thudichum's earlier work (1875) and that of Gutnikov (1896-7) should also be mentioned. Other more recent analyses and general discussions of the brain which include classifications of the phosphatids are those of Waldemar Koch (1904), of Coriat (1905) and of Frankel (1909a). The basis of classification which Thudichum introduced has proved to be very satisfactory and has continued in use with but slight modifications.

Since the phosphatids resemble the fats in their solubilities, and in some other properties, it has been found convenient to discuss these groups together with cholesterins and cerebrosides under the comprehensive name of "lipoids," or "fat-like substances." Ivar Bang defines lipoids as, "compounds which are soluble in organic solvents such as ether, alcohol, chloroform and benzol."

Bang's book, published in 1911, is freely used in the preparation of this article and his classification is followed. Rosenheim (1909) presented certain "Proposals for the Nomenclature of the Lipoids," in which several names are discarded, and the group divisions are fitted to those which are retained. The classification does not materially differ from that of Bang.

The phosphatids are in every way the most important lipoids. They are of great physiological interest, both as food constituents of specific importance and as cell constituents with significant functions. Apparently they are primary constituents of cells, that is, are found in all cells, and are necessary for the life of the cell. They are interesting in their chemical relations and are as difficult to obtain pure as are the proteins.

The name "phosphatid" was proposed by Thudichum to signify that we have here bodies similar to phosphates though not just like them. Phosphoric acid was considered to be the central group of the molecule, with which are combined an alcohol, fatty acids and a nitrogenous base. The alcohol is at least nearly always glycerin, and the base is mainly choline. If there be one such phosphoric acid molecule only, the compound is a monophosphatid; two such, united, may form a diphosphatid. Further, there may be one or

two, perhaps three, possibly more nitrogenous groups making monamino, diamino, etc., compounds. The phosphatids are classified on this basis. Thus, if on elementary analysis a substance of this class is shown to have the relative number of atoms of nitrogen and phosphorus such that N:P=2:1, it is placed in the diamino-monophosphatid group. These names are still used although the present conception makes glycerin more centrally significant in the molecule than Thudichum thought it to be.

Bang's classification makes use of a difference pointed out by Fränkel (1909b) by which the phosphatids which contain an unsaturated fatty acid form one class, and those which contain only saturated fatty acid radicals form another. The former, in distinction from the latter, are semisolid or viscous; they do not crystallize; they oxidize in the air, they are easily decomposed and they readily react with other substances. They are for these reasons particularly difficult to obtain pure, and doubtless most of the preparations that have been examined have been mixtures. According to Erlandsen, the cadmium chloride method of preparation causes some decomposition.

The following is Bang's classification including the best-known phosphatids:

BANG'S CLASSIFICATION OF PHOSPHATIDS

A. Unsaturated Phosphatids

I. Monamino-monophosphatids, (N:P, 1:1)
Lecithin, cephalin and myelin.

II. Monamino-diphosphatids, (N:P, 1:2)
Cuorin, liver phosphatid and monamino-diphosphatid from egg-yolk.

III. Triamino-diphosphatids, (N:P, 3:2)

B. Saturated Phosphatids

I. Diamino-monophosphatids, (N:P, 2:1)
Sphingomyelin and diamino-phosphatids from muscle, from egg-yolk and from horse pancreas.

II. Triamino-monophosphatids, (N:P, 3:1)
Neottin and carnaubon.

III. Protagon.

C. Insufficiently Characterized Phosphatids

D. Plant Phosphatids

A. UNSATURATED PHOSPHATIDS

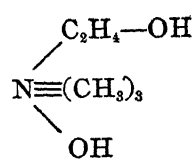
1. MONAMINO-MONOPHOSPHATIDS
LECITHIN, OR LECITHINS

Occurrence. The best known of the phosphatids and the one which is apparently most widely distributed in the animal kingdom is lecithin. However, it is now recognized that not all of the substances which have been reported as lecithin should be given this name. It is only within quite recent years that sufficiently discriminating work has been done to differentiate lecithin from certain other phosphatids. It is possible that it is a primary constituent of animal cells, but it is not impossible that it is sometimes lacking and its place taken by another phosphatid. Apparently it is not present in any vegetable substance. Its identity is little to be questioned, however, as found in heart muscle (Erlandsen, 1906, 1907; MacLean, 1908a), muscle of the extremities (Erlandsen, 1906, 1907), egg-yolk (Stern and Thierfelder, 1907; Erlandsen, 1907; MacLean, 1909c) and liver (Baskoff, 1908).

MacLean (1912b), using special purification processes, proves the principal phosphatid of kidneys and of muscle to be at least lecithin-like in its nitrogen and phosphorus content.

The discovery of lecithin was made by Gobley, who found it in egg-yolk in 1846, in the brain of hen, sheep and man in 1847, in the eggs and milt of carp in 1850, in the blood of ox and man in 1851, and in bile in 1856. He more fully studied that in human brain in 1877. (Gobley, 1846, 1847, 1850a, 1850b, 1851, 1856, 1877.)

Constitution. Gobley recognized the existence in lecithin of glycerophosphoric acid, of fatty acid, and of nitrogen in an NH_3 group. The nitrogenous group was thought by Liebreich (1865) to be neurine, but Strecker (1868) showed it to contain oxygen and to be choline. It is now recognized as being mainly choline.

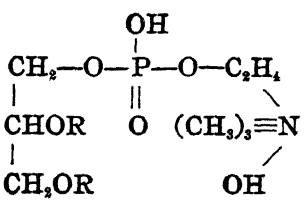


(See also Bergell, 1900, 1901.)

MacLean (1908a, 1909a, 1909c) has shown that not all of the nitrogen in lecithin is present as choline, and, moreover, that lecithins from different sources do not agree in the proportion of choline they contain. Very careful examination of lecithin from heart

muscle showed not more than 42.6 percent of the nitrogen to be present as choline, while in commercial lecithin 80 percent and in that from egg-yolk 66 percent of the nitrogen was present in this form. MacLean was led to feel that some of the nitrogen must be in the form of amino acid. Trier (1912, 1913b) has isolated from the hydrolytic products of egg lecithin, as well as from related compounds of plant origin, a compound of amino-ethyl-alcohol which he thinks may be the mother substance of choline, and which he names "colamin."

The structure of the lecithin molecule was early studied by Diaconow (1867b, 1868a, 1868b), by Strecker (1868) and by Gilson (1888). Diaconow held that the choline is bound with the phosphoric acid in salt-like union, while Strecker and Gilson believed that it is ester-like. The constitution suggested by Strecker is practically that which is now generally accepted.



In this formula R stands for a fatty acid radical. Two of these radicals are supposed to take the place of the hydrogen in two of the OH radicals of the tribasic alcohol, glycerin, and the phosphoric acid that of the other. This formula is supported by the observations on optical activity as made by Ulpiani (1901) and by Willstätter and Lüdecke (1904), but not by the recent study of Malengreau and Prigent (1912) on the rate of cleavage of the different radicals in acid hydrolysis. According to these observations, the splitting off of choline and of the fatty acids takes place at the same time, and much more rapidly than the phosphoric acid is freed from its glycerophosphoric acid combination. Hence it is thought that the linkings of the phosphoric acid with other residues (glyceryl and choline) are not of the same nature, as they would be according to the above formula.

Of the phosphatid components the fatty acids are of most value in distinguishing one phosphatid from another. Thudichum thought that oleic acid is characteristic of lecithins, and that it is associated with some other, usually palmitic or margaric acid. Henriques and Hansen (1903) showed that there must be some acid present more unsaturated than is oleic acid. Cousin (1903) and Erlandsen (1906, 1907) both speak of linoleic acid as a phosphatid

constituent. Attempts to identify the acid by its iodine number have brought results which cannot at present be reconciled. Of course oxidation, which so easily takes place, rapidly reduces the iodine number. Bang's conclusion, after considering all the evidence, is that there are in lecithin two fatty acids, one of which is stearic and the other an as yet undetermined unsaturated acid. The saturated acid may be palmitic (Serono and Palozzi, 1911).

These disagreements and uncertainties with regard to the constituents of lecithin are doubtless due in part to the fact that the pure compound has not been obtained, since lecithin so readily oxidizes, and is so difficult to free from other phosphatids, fats, etc. It is quite doubtful if the substances examined were individual compounds. Bang says that elementary analysis has shown Merck's preparation to be quite impure and unsuited to scientific work; and that the preparation of the proprietary product known as "agfa-lecithin" by Bergell's method, which makes use of the $CdCl_2$ precipitation, has been shown by Erlandsen to cause a serious decomposition. Hence conclusions which have been drawn on the basis of work with these products are of little value.[1] Bang considers that no suitable method of preparation has been described except that of Erlandsen.

It cannot be said, finally, whether there is but one lecithin or whether there are several lecithins isolated from animal products by the same process.

Elementary Analysis. The elementary analyses and empirical formulae reported by different workers are nearly alike, although not identical. A few are quoted here:

ELEMENTARY ANALYSES OF LECITHINS—Percent

Author	Date, reference	Source of lecithin	C	H	N	P	Formula
Thudichum	?	Brain	66.75	18.67	1.81	4.00	$C_{43}H_{84}NPO_9$ (1)
Koch	1902b	Brain	64.03	10.4	1 8	3.79	.....
Erlandsen	1906, 1907	Muscle of heart	66.29	10.17	1.87	3.95	$C_{43}H_{80}NPO_9$
MacLean	1908a	Muscle of heart	66.27	10.32	1.85	3.975	.....
Erlandsen	1907	Muscle of thigh	65.96	10.20	1.82	3.93	$C_{43}H_{80}NPO_9$
Stern and Thierfelder	1907	Egg-yolk	64.63	10.96	2.08	3.97	.....
Mac Lean	1909a	Egg-yolk	64.18	10.6	1.876	3.95	.....
Baskoff	1908	Liver	64.64	10.71	1.95	4.00	.....

(1) Quoted through Bang (1911).

(1) Altchul's (1912) assertion that "Agfa-lecithin" is not made by Bergell's method, but by a method worked out by himself, which gives a pure product, is answered by Bang (1912) by saying that he based his statement as to the method used on the authority of the "Agfa" company.

Properties. Lecithin is a white, yellow, or orange-colored substance, usually amorphous, and of a waxy consistency when dry. Some have obtained it in crystalline form, the crystals being thin flakes. It is very hygroscopic, and in the air it takes up moisture, and softens to a semifluid mass. It also readily takes up oxygen from the air, and in doing so grows darker in color. Unlike the fats, lecithin becomes wet and sinks in water. Gradually it takes up water and swells to a gelatinous mass, and finally spreads to an opaque, colloidal solution. Lecithin is precipitated from this colloidal solution by certain acids and salts, and precipitation is prevented by other salts. It is thought that the tendency of phosphatids in general to pass into the colloidal state, and their properties as colloids, may be significant in their functioning within the cells. The precipitating power seems to be due to the individual ions and dependent on their concentration. It is a reversible reaction, and the total effect is a summation of the effects of the individual ions present. Quantitative studies of such precipitations of lecithin and other lipoids have been made by W. Koch (1902a, 1903, 1907a, 1909b, 1910b), Koch and MacLean (1910), Koch and Mostrom (1910), Koch and Pike (1910), Koch and Williams (1910), Porges and Neubauer (1907), Long (1908), Long and Gephart (1908a) and Feinschmidt (1912). See also the physicochemical studies of Handovsky and Wagner (1911) concerning the reactions of such emulsions with inorganic salts and with proteins.

Lecithin is easily dissolved by alcohol, either hot or cold, and is precipitated from this solution by water. It is soluble also in ether, chloroform, carbon bisulphide, benzene and some other organic solvents, but nearly insoluble in cold acetone and in methyl acetate. The power of lecithin (and other lipoids) in such organic solvents, to take up organic substances, has recently been investigated by Loewe (1912a, 1912b, 1912c, 1912d) and is attributed to adsorption. R. Cohn (1913) thinks that on longer action the adsorption becomes so intensive that probably a chemical adsorption results.

According to Ulpiani (1901), and to Willstätter and Lüdecke (1904), lecithin shows by its optical activity that it has an asymmetric molecule. Paul Mayer (1905,1906b) separated the racemic form under the influence of an enzyme (lipase) into dextro- and laevo-lecithin, which then behaved differently toward the lipase, the laevo-lecithin remaining unchanged while the dextro-lecithin broke down into fatty acids and dextro-glycerophosphoric acid.

Lecithin is readily saponified by alkalis and especially by baryta, yielding fatty acids, glycerophosphoric acid and choline. The cleavage with dilute acids is quite slow. Casanova's (1911) observations indicate that the first step in the cleavage resulting from the taking up of water in the presence of oxygen is a separation of choline and glycerophosphoric acid esters of the fatty acids, further taking up of water being required for the cleavage of these esters. Malengreau and Prigent (1912) found that only about 70 percent of the choline and fatty acids was split off in two hours by 0.1N sulphuric acid, that after 13¾ hours they were nearly all split off, but the cleavage of the glycerophosphoric acid was much more slow, and was still incomplete after 72 hours. Lecithin is cleaved by digestive ferments.

Compounds. Lecithin shows more power to enter into combination with other substances than do most organic compounds. These combinations are of different kinds; sometimes additions in molecular relation, forming well-characterized compounds, and sometimes in other combinations of which the nature is not known, which may be chemical complexes or may be adsorption products. Thudichum suggests that it may be of considerable physiological significance that the phosphatids generally react with so many kinds of substances and are thereby changed, and that these reactions are so dependent on the concentrations of the reacting substances.

Combinations of lecithin with inorganic acids, with some bases, and with both inorganic and organic salts have been studied. These seem to be usually chemical and perhaps mainly addition products, though it has been shown in some cases that partial decomposition accompanies the taking up of salt.

Bang gives the following summary of the classes of organic compounds with which lecithin combinations have been made; (1) glucosides, such as phlorizin, salicin and amygdalin, (2) alkaloids, such as chlorides of morphine and nicotine and sulphate of strychnine, (3) toxins, as cobra poison and bee poison, (4) cholesterin, (5) enzymes, (6) dyes, (7) carbohydrates, (8) proteins. These substances have not been very well studied as yet and only the last two need be considered here.

Compounds of Lecithin and Carbohydrate. Apparent combinations of lecithin and carbohydrate have been prepared. For example, if an alcoholic solution of lecithin and glucose be evaporated to dryness, a substance is obtained which shows different solubilities from either component, which is taken as indication that a chemical union has taken place. Similar substances are said to have been

isolated from organs and from blood. These preparations give glucose on decomposition, also the cleavage products of lecithin; but as they are not constant in composition, nor permanent in their solutions, or under repeated evaporation, it seems probable that no chemical union exists but that we have here simply an example of the power lecithin shows to change by its presence the solubility of other compounds. These artificial preparations have been spoken of as identical with Drechsel's jecorin, but that idea must immediately be given up when it is shown that jecorin always contains sulphur and sodium. However, jecorin may be also a similar loose combination, or mixture of sugar with a phosphatid or its decomposition products.

Jecorin was first found by Drechsel (1886), and has usually been obtained by the use of his method. Drechsel isolated it from the liver of a horse, and the following year Baldi (1887) found it in the liver of the rabbit and the dog, in beef spleen, horse blood, horse muscle and human brain. He said it was present in largest amount in liver and next in spleen. Since then it has repeatedly been isolated from liver (P. Manasse, 1895; Meinertz, 1905; Siegfried and Mark, 1905; P.Mayer, 1906a; Mark, 1907; Waldvogel and Tintemann, 1906; Baskoff, 1908, 1909a, 1909b) and from blood (Henriques, 1897; Bing, 1899; P. Mayer, 1906a), and is also reported from adrenals (P. Manasse, 1895), spleen (Waldvogel and Tintemann, 1906) and bone marrow (Otolsky, 1906). Both smooth and striated muscles showed a very little jecorin in Erlandsen's (1906,1907) analyses.

The nature of jecorin is not established. All the preparations examined contained, in addition to phosphorus and other constituents of lecithin, sulphur and sodium and a reducing substance which has been identified as glucose. Bing (1899) looked upon it as a compound of lecithin and glucose, and it has been investigated as such. However, it cannot be simply such a compound, on account of the sulphur and the sodium content, as has been said, and it is doubtful if the lecithin is chemically united with the glucose. It may be that the union of the reducing substance with the lecithin-like fraction or fractions takes place at the time of their simultaneous precipitation. At least, it seems probable that the various substances that have been obtained are not identical, for they differ in elementary composition, and contradictory properties have been reported.

Baskoff (1908), after a review of the subject, and careful experimental investigation of Drechsel's jecorin purified in several ways, and a consideration of other products separated during the

processes, concludes that "Drechsel's jecorin may be characterized as a lecithin-like complex with about 14 percent glucose, which also always contains sulphur and an inorganic substance," and that there are other jecorin-like bodies not identical with it. The close similarity in chemical composition of his several purified products argues against such an indefinite mixture of substances as Paul Mayer, Meinertz, Siegfried and Mark, and A. Mayer and Terroine have suggested. (References as previously given and A. Mayer and Terroine, 1907.)

Baskoff finds the relation of N:P=2:1, corresponding to a diamino-monophosphatid. Others have found different ratios.

Lecithin-Protein Compounds, or Lecitho-Proteins. The vitellin isolated from egg-yolk contains considerable lecithin (or other phosphatid) from which it is freed with great difficulty, and there is some question as to whether it should not be looked on as a phosphatid-globulin. However, there seems to be sufficient evidence that not all of the phosphorus is present as phosphatid but that we have here a nucleoalbumin, still containing phosphorus after all phosphatid is removed. Hoppe-Seyler and others consider that the original vitellin is chemically combined with lecithin and that the phosphatid-free vitellin is therefore to be looked on as a denatured compound. According to T. B. Osborne and Campbell (1900b), the so-called ovovitellin is a mixture of several vitellin-lecithin combinations containing 15-30 percent of lecithin. The chemical union is not proved, nor is the identity of the lecithin present, which may be the diamino-phosphatid which Erlandsen found in egg-yolk.

Other lecithin-protein compounds have been discussed under the name of lecithalbumin. Liebermann (1891a, 1891b, 1893a, 1893b) isolated what he called lecithalbumins from the mucous membrane of the stomach (hog), from kidney (sheep), liver (lamb), lungs and spleen. The methods used in preparing and handling these substances were not sufficiently discriminating to prove their nature. Several observers think that the phosphatids of the serum and of chyle are in combination with globulin.

According to Erlandsen's interpretation of his extractions from muscle, the lecithin found there is entirely free or in easily cleavable condition, while the diamino-phosphatids are in some complex union with proteins or other substances so that they cannot be extracted until the proteins have been precipitated with alcohol. Microscopical observations indicate that the phosphatids are in some kind of union with other cell constituents.

Bing (1901) discusses the solubilities of a variety of lecithin compounds. For an extended general review of literature on lecithin see Merck (1912).

CEPHALIN

Cephalin was first studied as isolated from brain by Thudichum (Thudichum, 1875; Thudichum and Kingzett, 1876), and has since been reported by W. Koch and his associates as found in various tissues and organs, and in milk and yeast, by Stern and Thierfelder in egg-yolk, and by Cousin, Falk and Fränkel and associates in brain and nerves. (W. Koch, 1902b, 1903, 1904, 1906; W. Koch and Goodson, 1906; W. Koch and Woods, 1905; W. Koch and Mann, 1907; Stern and Thierfelder, 1907; Cousin, 1906; Falk, 1908; Fränkel and Neubauer, 1909; Fränkel and Dimitz, 1909.) Erlandsen did not find it in either kind of muscle. According to Thudichum, it is the principal phosphatid in the brain, and Falk's analysis of peripheral nerves shows considerably more cephalin than lecithin. It is doubtful if cephalin has ever been obtained in the pure state. Koch reports that "agfa" lecithin is two-thirds cephalin. Koch, however, at a later date, abandoned the method which served as the basis for the quantitative separation of lecithin and cephalin. (Jour. Am. Chem. Soc. 31, 1909, p. 1349.)

Cephalin is a highly unsaturated monamino-monophosphatid. It is autoöxidizable. The nitrogenous base is probably not choline, but a base of lower CH_3 content (W. Koch, 1902b; Fränkel and Neubauer, 1909).

Baumann (1913) reports that this base exists in cephalin as a primary amino group, and Renall (1913) recognized in cattle-brain cephalin an amino ethyl alcohol, which he considers a characteristic constituent of cephalin.

The base is united with glycerophosphoric and fatty acids, the latter, according to Cousin (1906) containing saturated acids, almost entirely stearic, and unsaturated acids of the linoleic series. Cousin worked with the brain of cattle.

Fränkel and Dimitz (1909) think that the cephalin of brain is a mixture of palmityl-cephalin and stearyl-cephalin, with more of the former. Parnas (1913) states that all of the fatty acid cleaved from cephalin by baryta is stearic acid. Falk (1908) says that the cephalin of the peripheral nerves is not the same as that of the brain.

Thudichum gave the name cephalic acid to the unsaturated acid, which he considered the distinguishing component of cephalins,

and which through its marked variability in composition imparts variability to cephalins. He also found a second base. Some investigators have found inorganic base elements, as Ca or K, which seemed to belong to the cephalins. The solubilities of the preparations reported by different workers do not agree.

Some of the elementary analyses reported are as follows:

ELEMENTARY ANALYSES OF CEPHALIN—Percent

Author	Date and Reference	Source of Cephalin	C	H	N	P	Formula
Thudichum	1901	Brain	60.00	9.38	1.68	4.27	$C_{42}H_{79}NPO_{13}$
Koch	1902b	Brain	59.5	9.8	1.75	3.83	$C_{42}H_{82}NPO_{13}$
Fränkel and Neubauer.	1909	Brain	62.05	9 85	1.69	3.45	.....
Falk [1].....	1908?	Nerve	57.0	9.1	1.94	4.4	.....
Stern and Thierfelder	1907	Egg-yolk	59.68	9.74	1.57	3.64	.....

(1) These figures are taken through Bang (1911a).

Bang gives as the probable formula, $C_{42}H_{80}NPO_9$; Hammarsten gives $C_{42}H_{82}NPO_{13}$. If there are several cephalins, the formulas and percentage compositions vary accordingly.

OTHER MONOPHOSPHATIDS

Other monophosphatids which may be mentioned here are the cephalin variations, the paramyelin ($C_{38}H_{75}NPO_9$) and the myelins ($C_{40}H_{75}NPO_{10}$) of Thudichum, a monophosphatid found by Erlandsen in the acetone solution from heart muscle, and vesalthin obtained by Pari (Fränkel and Pari, 1909; Fränkel, Linnert and Pari, 1909) as the $CdCl_2$ salt, $C_{32}H_{63}NPO_9.CdCl_2$, from the corresponding extract from pancreas.

II MONAMINO-DIPHOSPHATIDS

According to Erlandsen, diphosphatids are regularly found in large amount in heart muscle, and only in small amount in the striated muscle. One or two have been found elsewhere in the animal body, but none have been fully studied. They have not been found in the brain.

CUORIN

For cuorin, found in heart muscle, Erlandsen gives the formula $C_{71}H_{125}NP_2O_{21}$, which implies a much larger molecule than that of lecithin. It is made up of glycerophosphoric acid, three fatty acids and a nitrogen-containing base that is not choline. The fatty acids are mainly highly unsaturated and are thought to belong to the linoleic or the linolenic acid series. Cuorin is even more autoöxidizable

than lecithin, and the properties are much altered by such oxidation. MacLean (1912a, 1912b) finds cuorin in horse kidney and muscle.

OTHER MONAMINO-DIPHOSPHATIDS

Other monamino-diphosphatids similar to cuorin, but not identical with it, have been obtained by Baskoff (1908) from horse liver, and by MacLean (1908b, 1909b) from egg-yolk. Elementary analyses of the three substances are given here:

ELEMENTARY ANALYSES OF MONAMINO-DIPHOSPHATIDS—Percent

Author	Date and Reference	Source	C	H	N	P	O	S	N:P
Erlandsen	1906, 1907	Heart	61.63	9.03	1.015	4.46	23.86	None	1:1.99
Baskoff ..	1908	Liver	61.12	8.95	1.23	4.00	(24.04)	0.6	1:1.47
MacLean .	1909b	Egg-yolk	59.12	9.44	0.812	3.59	27.048	....	1:2

Baskoff called his compound "heparphosphatid." It contained sulphur. The N-component was thought to be other than choline, but was undetermined. It had a lower fatty acid content than lecithin. It did not react with sugar. MacLean found his compound in about equal amount with cephalin in egg-yolk.

III TRIAMINO-DIPHOSPHATIDS

Triamino-diphosphatids have been obtained only by Fränkel and his co-workers as $CdCl_2$ compounds (Fränkel and Nogueira, 1909a, 1909b; Fränkel and Linnert, 1910). The methods used are unreliable. These compounds were obtained from kidney and from brain. Only that from the brain, which is called "sahidin" has been studied in detail. From hydrolysis it appears to be a compound of choline with glycerophosphoric acid and fatty acids, the latter being of both saturated and unsaturated type. It is quite conceivable that the compound under examination was a monamino-monophosphatid of the lecithin type containing a nitrogenous substance as an impurity.

B. SATURATED PHOSPHATIDS

I. DIAMINO-MONOPHOSPHATIDS

This class of compounds appear to be primary constituents of cells, but they have not been studied sufficiently to furnish definite conceptions as to their constitution or their relations to one another.

SPHINGOMYELIN

Thudichum, and Rosenheim and Tebb (Rosenheim and Tebb, 1907, 1908a, 1908b, 1908c, 1909a, 1909c, 1910) have felt that they showed the so-called "protagon" of the brain to be mainly a mixture of a diamino-monophosphatid, which Thudichum named sphingomyelin, and cerebrosides. Rosenheim and Tebb found the same characteristics in the substance isolated from the cortex of the adrenals, but with a smaller amount of sphingomyelin. Thudichum gives the formula $C_{52}H_{104}N_2PO_9+H_2O$ for sphingomyelin. Rosenheim and Tebb (1908c) report an elementary analysis with 3.46 percent P, from which Bang computes the formula $C_{49}H_{104}N_2PO_{10}$. If the work of these two sets of observations is correct, sphingomyelin is, with carnaubon only, an exception among the phosphatids in that it contains no glycerin, and therefore is not a glycerophosphoric acid compound. It does show phosphoric acid, fatty acids (perhaps only one, which Thudichum identified as an isomer of ordinary stearic acid) and choline (or neurine) and a crystalline alcohol. Rosenheim and Tebb (1908b) made a study of the peculiar property of sphingomyelin by which it separates from its pyridine solution, or a pyridine solution of protagon, in doubly refracting spheroid crystals which are strongly laevorotatory, the dextrorotation of the original protagon solution thus being gradually lessened and finally changed to laevorotation. Since this substance is probably widely distributed in cellular tissues, it is desirable that it should receive much further study.

OTHER DIAMINO-MONOPHOSPHATIDS

Other diamino-monophosphatids are the apomyelin and amidomyelin of Thudichum, a phosphatid isolated from liver by Baskoff (1908) which showed the ratio P:N=1:2.55, one taken from kidney by Nogueira for which the formula $C_{34}H_{72}N_2PO_{10}$ is given, and two others the properties of which are reported as resembling those of sphingomyelin. Of these, that of Stern and Thierfelder (1907), was obtained from egg-yolk, and the elementary analysis showed 3.22 percent P and a ratio P:N=1:1.9. One of the compounds which Erlandsen obtained as a $CdCl_2$ combination, but was not able to isolate free, seemed to have the formula $C_{40}H_{75}N_2PO_{12}$. It was obtained from both types of muscle, though apparently it was not present in the free state but in protein combination. Cleavage indicated but one molecule of fatty acid and probably two basic radicals. The fatty acid was an oxyacid. Otherwise it much resembled lecithin.

Burow (1910) finds three iron-containing phosphatids in the spleen of cattle and of man. Only one of these was obtained in sufficient amount for analysis and that proved to be a diamino-monophosphatid. The name "ferroid" was proposed to show its iron-lipoid character.

Baskoff's (1908) analyses of purified jecorin indicate that that compound may be a diamino-monophosphatid (see p. 65).

II. TRIAMINO-MONOPHOSPHATIDS

The triamino-monophosphatids which have been reported are the neottin of egg-yolk, found by Frankel and Bolaffio (1908), and the carnaubon of kidney, found by Dunham and Jacobson (1910).

NEOTTIN

Neottin is a saturated compound, optically inactive. It is thought to contain choline and three saturated fatty acids, stearic, probably palmitic and perhaps cerebronic.

CARNAUBON

Carnaubon differs decidedly from all other animal phosphatids that have been examined, except jecorin, in that it contains a sugar (galactose or aminogalactose) which is but incompletely split off in simple hydrolysis and therefore must form an essential part of the phosphatid molecule. Such compounds are common in plants. No glycerin is found in carnaubon, and Dunham and Jacobson suggest that the structure may be similar to that of lecithin, but with the sugar in the place of glycerin. Three fatty acids were found, carnaubic, stearic and palmitic, with phosphoric acid and choline. Assuming that carnaubon is made up of aminogalactose, these three fatty acids and one phosphoric acid in combination with two choline groups, the formula $C_{74}H_{150}N_3PO_{13}$ is proposed.

MacLean (1912a, 1912-13) isolated from horse kidney a substance having all the properties of this compound of Dunham and Jacobson, but it was a diamino-monophosphatid. He thinks it probable that carnaubon is not a tri-, but a diamino-monophosphatid and that the methods used by Dunham and Jacobson were inefficient to obtain a pure substance. By water extractions MacLean (1912a, 1912b) separates water-soluble substances which contain but little phosphorus, and are not of the nature of ordinary phosphatids, but are easily confused with them in the processes ordinarily used for isolation of phosphatids. As these substances have a high nitrogen content, it may be that several of the substances hitherto described as containing large percentages of nitrogen are really mixtures of

simpler bodies with these. He recommends a purification by a process of emulsification with water and precipitation with acetone.

III. PROTAGON

For a long time the name "protagon" was in use for a substance isolated from brain and thought to be the principal, perhaps the only, phosphatid of brain. It was found also in many other parts of the body. That these preparations were crystalline and fairly constant in composition even after recrystallization justified the belief that protagon was a chemical unit; later work, however, has shown that such a conception is untenable. Since the first finding and naming of protagon by Liebreich in 1865 it has received much attention. A list of references is given below.

The question of protagon being the main or only constituent of the brain was satisfactorily answered by Frizzell's analyses, reported by Chittenden, and especially by the abundant evidence from Thudichum's work. Thudichum also showed that it is a mixture, and that it does not contain lecithin. Thudichum's work, however, seems not to have met with due recognition until after his death. Further evidence against the chemical entity of protagon has been produced mainly by Gies and his associates, and by Rosenheim and Tebb. They have shown that it is made up of phosphorus-rich and phosphorus-poor components mixed in variable proportions. Kossel and Freytag had already recognized the presence of cerebrosides, which are phosphorus-free compounds consisting of the sugar galactose, fatty acids and a nitrogen complex. Thierfelder and his associates have separated and studied cerebron, another phosphorus-free compound. The phosphorus compound was identified by Thudichum and by Rosenheim and Tebb, as sphingomyelin, but it is perhaps not a single phosphatid. Sulphur has usually been found in protagon, and apparently in organic combination, and Koch thought that he had evidence of a complex containing an ethereal sulphuric acid combined with a phosphatid and a cerebroside, as one of the substances present in the mixture. Fränkel concludes that protagon is a mixture of members of the group which he designates "galacto-phospho-sulphatids," or combinations of phosphatids and sulphatids with galactose. It is not to be looked upon as a chemical unit.

References on protagon: Liebreich, 1865; Diaconow, 1867a; Gamgee and Blankenhorn, 1879a, 1879b, 1879c, 1880; Baumstark, 1885; A. Kossel, 1891b; A. Kossel and Freytag, 1893; Ruppel, 1895; Chittenden, 1897; Noll, 1899; Wörner and Thierfelder, 1900; Kita-

gawa and Thierfelder, 1906; Ulpiani and Lelli, 1902; Barbieri, 1905; Lesem and Gies, 1903; Cramer, 1904; Orgler, 1904; Posner and Gies, 1905; Lochhead and Cramer, 1907; Gies, 1907; Steel and Gies, 1907b; Wilson and Cramer, 1908; Cohen and Gies, 1908; Rosenheim and Tebb, 1907, 1908a, 1908b, 1908c, 1909a, 1909c, 1910; W. Koch, 1907b, 1910a, 1912; Fränkel, 1908.

D. PLANT PHOSPHATIDS

Apparently phosphatids are as widely distributed (and therefore probably essential) in plant cells as in animal cells, and are as varied in their make-up, though the work of differentiation and classification has not yet been carried even as far as it has for those of animal origin. Nearly all of the investigations we have found reported have been made by E. Schulze and E. Winterstein and their associates (Schulze and Steiger, 1889; Schulze and Likiernik, 1891a, 1891b; Schulze and Frankfurt, 1894; Schulze, 1895, 1897, 1907, 1908a, 1908b; Schulze and Winterstein, 1903; Hiestand, 1906; Winterstein and Hiestand, 1906, 1908; Winterstein and Stegmann, 1909a, 1909b; Winterstein and K. Smolenski, 1909; K. Smolenski, 1909; Schulze and Pfenninger, 1911; Trier, 1911, 1913a, 1913b, 1913c, 1913d). A few other articles should be mentioned, especially that of Njegovan (1911); also those of Wintgen and Keller (1906); Parrozzani (1909); Vorbrodt (1910) and Bernardini (1912).

It was at first supposed that all the phosphorus-containing fat-like substances obtained were identical with those of animal tissues, and, as for the latter, so for these, the name lecithin was used, and the cleavage products somewhat supported the idea; but it was later shown that there are several different phosphatids here and that the true lecithins are not found at all in plants. The phosphatids of the two kingdoms are essentially different, in that vegetable phosphatids nearly or quite always contain a sugar, apparently firmly bound and in constant stoichiometric relation with the rest of the molecule, such as is not the case in animal phosphatids, with the probable exception of jecorin, and perhaps carnaubon. The amount of carbohydrate found has been widely different in different preparations, suggesting that a part, at least, of it is present as a phosphatid-sugar combination such as the lecithin-sugars mentioned above. The plant phosphatids contain, together with the sugar, glycerophosphoric acid, fatty acids and choline, and sometimes other nitrogenous residues, either basic or amino acid.

ARTIFICIAL SYNTHESIS OF PHOSPHATIDS

Glycerophosphates have been made by several investigators, and they have found extensive use as drugs. See Adrian and Trillet (1897, 1898), Lumière, A. L., Lumière and F. Perrin (1901), Carré (1904), Willstätter and Lüdecke (1904), Power and Tutin (1905), Tutin and Hann (1906), Neuberg and Kretschmer (1911), Langheld (1910, 1911, 1912), DuBois (1914), and also a review of literature by Merck (1911).

The question of the identity of the synthetic products with the glycerophosphate of lecithin was considered by Willstätter and Lüdecke, Tutin and Hann, and Power and Tutin, with evidence that they are not identical, and that the difference is in the structure of the molecule. Power and Tutin say that, in the substances handled, the mono-ester, $C_3H_5(OH)_2O.PO(OH)_2$, has often been contaminated with the di-ester, $C_3H_6OH\begin{matrix}O\\ \diagup\ \diagdown\\ O\end{matrix}PO(OH)$. Tutin and Hann conclude that both the synthetic and the natural products are mixtures of the asymmetric or α-acid, $CH_2O.PO_3H_2$,

$$\begin{matrix}|\\ CH.OH\\ |\\ CH_2.OH\end{matrix}$$

and the symmetrical or β-acid, $CH_2.OH$

$$\begin{matrix}|\\ CH.O.PO_3H_2\\ |\\ CH_2.OH\end{matrix}$$

DuBois (1914) discusses these and other possible glycerophosphates, and gives in detail the properties of such as are known. Considering the evidence brought forth by others in comparing the natural and synthetical products leads him to the "conclusion that the synthetical glycerophosphates produced at low temperatures (100-110°), and the natural glycerophosphates obtained from lecithin are almost identical, and in all probability, a mixture of the α- and β-isomerides, in which the α-isomeride predominates."

According to Francois and Boismenu (1913) commercial calcium glycerophosphate may be a mixture of salts of 5 forms of the acid, namely the tri-ether, and the α- and β- forms of both di- and mono-ethers. The calcium salt of the tri-ether, however, is so difficultly soluble that it is not usually permitted by the manufacturer to be present in the commercial article.

THE PHOSPHORUS OF PHOSPHATIDS

In the phosphatids, and in no other natural products, so far as known, phosphorus is present as glycerophosphoric acid, a glycerin ester of orthophosphoric acid. The most ready cleavage sets free this glycerophosphoric acid, and further cleavage produces free orthophosphoric acid. This relation seems to be unquestioned.

See Imbert and Belugon (1897), with regard to the reactions of glycerophosphoric and phosphoric acids with bases, and Malengreau and Prigent (1911) with regard to the hydrolysis of glycerophosphoric acid.

For general discussions on the phosphatids see Thudichum (1901), Hiestand (1906), Bang (1909), Fränkel (1908, 1909a), MacLean (1909d), Bang (1911a) and Merck (1911, 1912).

PART II.

THE PHOSPHORUS COMPOUNDS OF FOODS

GENERAL DISCUSSION

A statement of the phosphorus content of a foodstuff is of slight value apart from a consideration of other nutrient constituents, but we can not, within the scope of this article, go into the matter of general composition of foods. In our selection of material for presentation in this section, therefore, we have sought to include especially data showing the connection of the phosphorus content of foods with other matters of interest, particularly as related to general type of food products, or to conditions of growth, preparation or manufacture; and also such material as is available showing the differential estimation of the various groups or kinds of phosphorus compounds in foodstuffs. For data on total phosphorus of foods see the works cited on p. 103.

Analyses of meats, milks, and eggs will be found in the section on Phosphorus of Animal Bodies and Products, and are not included here except as they appear in miscellaneous tables.

From the following tables of Forbes, Beegle and Mensching (1913) we note that among the milling products of wheat the phosphorus is contained principally in the byproducts which are used as foods for live-stock. The white flour is that portion of the grain of wheat which contains the least phosphorus. Wheat gluten, such as is used as a diabetic flour is also poor in phosphorus. The bran contains more phosphorus than any other part of the kernel.

For further details regarding the phosphorus constituents of wheat see Osborne and his associates, p. 91, Rengniez, p. 78, Rising, p. 79, Ames and Boltz, p. 96-98, and Swanson, p. 80, of this work; also Girard (1884), Girard and Lindet (1903), Balland (1903), Surmont and Dehon (1903, 1904) and Fauvel (1907); also references on p. 103 to general works on food analysis and nutrition.

Corn contains less phosphorus than do oats and wheat, the pearl hominy and bolted corn meal used by human beings containing less phosphorus than the whole grain. Gluten feed contains more phosphorus than does the whole corn, and distiller's grains about the same as corn.

Kafir corn contains less phosphorus than does Indian corn, while polished rice is very poor in phosphorus, about the same as pearl hominy. Rice polish, however, which is fed to live-stock, is exceedingly rich in phosphorus.

On a dry basis the fruits are very low in phosphorus; such vegetables as onions, cabbage, beets, and potatoes contain much more.

Among various kinds of roughage, leguminous forage contains considerable phosphorus, as also does blue-grass. Timothy hay, corn stover and wheat straw contain much less. The phosphorus content of all sorts of roughage is much affected by the soil.

Leguminous seeds are characteristically rich in phosphorus, much richer than the leaves and stems of the same species, while the oil meals are still richer, cottonseed meal excelling linseed oil meal in this regard.

MINERAL ELEMENTS OF CEREAL PRODUCTS—Parts per 100 of Dry Substance (Forbes, Beegle and Mensching, 1913)

	Potassium	Sodium	Calcium	Magnesium	Sulphur	Chlorine	Phosphorus	Inorganic phosphorus	Organic phosphorus
Wheat	.590	.035	.056	.142	.224	.095	.425	.038	.387
Wheat flour	.058	.127	.022	.019	.168	.081	.102	.017	.085
White bread	.156	.583	.038	.004	.198	.958	.135	.043	.092
Wheat bran	1.464	.223	.139	.590	.297	1.000	1.233	.034	1.199
Wheat middlings	1.147	.186	.108	.430	.263	.029	.984	.069	.915
Wheat germ	.323	.788	.078	.372	.355	.077	1.147	...	...
Wheat gluten	.007	.031	.085	.049	1.000	.055	.220	.037	.183
Red dog flour	.425	.733	.134	.324	.285	.156	.928	.098	.830
Corn	.396	.030	.014	.126	.171	.073	.303	.028	.275
Corn meal, bolted	.192	.113	.015	.122	.122	.070	.264	.019	.245
Corn bran	.410	.000	.030	.088	.124	.052	.156	.031	.125
Pearl hominy	.153	.000	.005	.036	.182	.052	.111	.019	.092
Gluten feed	.272	.461	.268	.239	.636	.098	.589	.106	.483
Distiller's grains, corn	.014	.154	.047	.054	.509	.065	.314	.056	.258
Distiller's grains, rye	.045	.077	.142	.195	.408	.028	.458	.018	.440
Brewer's grains	.185	.278	.169	.172	.419	.062	.503	.162	.341
Malt sprouts	.219	1 458	.159	.194	.864	.389	.746	.471	.275
Oats	.460	.184	.112	.130	.214	.077	.434	.059	.375
Kafir corn	.288	.066	.013	.142	.186	.117	.271	.012	.259
Rice	.040	.032	.009	.028	.114	.040	.104	.003	.101
Rice polish	1.279	.124	.030	.741	.189	.151	1.684	.028	1.656

The animal products are, on a dry basis, rich in phosphorus, even whey containing notable amounts, while, of course, such foods as tankage, which contain some bone, are much richer than any other foods in phosphorus. Milk and eggs do not differ greatly in phosphorus content. Both are rich in phosphorus, and contain much more of this element than does meat.

MINERAL ELEMENTS OF FRUITS, VEGETABLES AND ROUGHAGE—Parts per 100 of Dry Substance (Forbes, Beegle and Mensching, 1913)

	Potassium	Sodium	Calcium	Magnesium	Sulphur	Chlorine	Phosphorus	Inorganic phosphorus	Organic phosphorus
Apple	.802	.066	.027	.033	.044	.037	.064	.033	.031
Prune	1.347	.045	.076	.056	.066	.050	.110	.098	.012
Banana	1.291	.240	.037	.129	.021	.421	.119	.089	.030
Date	.667	.115	.084	.086	.087	.285	.077	.037	.040
Onion	1.442	.097	.261	.136	.601	.183	.323	.210	.113
Cabbage	2.484	.028	.590	.209	.901	.243	.262	.136	.126
Potato, sweet	1.208	.061	.084	.215	.117	.069	.186	.138	.048
Potato, white	1.547	.175	.027	.331	.141	.055	.270	.130	.140
Mangel wurzel	3.870	.714	.131	.358	.224	1.380	.260	.174	.086
Beet pulp	.347	.185	.729	.283	.138	.048	.069	.006	.063
Clover hay	1.840	.067	1.236	.292	.190	.259	.183	.080	.103
Soy bean hay	1.774	.145	1.378	.692	.259	.084	.237	.121	.116
Cowpea hay	.873	.722	2.029	1.096	.352	.167	.283	.152	.131
Alfalfa hay	.832	.489	1.130	.400	.298	.161	.238	.122	.116
Timothy hay	.613	.345	.192	.111	.162	.199	.123	.052	.071
Millet hay	1.338	.099	.326	.262	.159	1.230	.173	.072	.101
Corn stover	1.847	.065	.507	.092	.187	.308	.102	.039	.063
Bluegrass	1.405	.141	.336	.240	.334	.234	.242	.142	.100
Wheat straw	.842	.237	.217	.063	.159	.209	.038	.015	.023
Agar agar	.132	.135	.780	.570	2.090	.040	.024	.003	.021

MINERAL ELEMENTS OF LEGUMINOUS SEEDS, NITROGENOUS CONCENTRATES AND ANIMAL PRODUCTS—Parts per 100 of Dry Substance (Forbes, Beegle and Mensching, 1913)

	Potassium	Sodium	Calcium	Magnesium	Sulphur	Chlorine	Phosphorus	Inorganic phosphorus	Organic phosphorus
Soy beans	2.095	.380	.230	.244	.444	.025	.649	.017	.632
Navy beans	1.390	.086	.235	.206	.224	.047	.429	.088	.341
Cowpeas	1.636	.189	.117	.243	.280	.047	.532	.023	.509
Peanuts	.061	.563	.068	.180	.254	.024	.399	.049	.350
Linseed oil meal	1.224	.282	.403	.544	.455	.095	.786	...	...
Cottonseed meal	1.811	.283	.291	.599	.536	.042	1.479	.078	1.401
Milk, skim	1.272	.488	1.336	.146	.357	.953	.979	.551	.428
Whey	2.762	.459	.721	.138	.139	1.948	.640	.402	.238
Mutton	.624	.214	.006	.062	.607	.235	.474	.230	.244
Eggs	.206	.389	.250	.059	.762	.621	.856	trace	.856
Tankage	.601	1.830	3.242	.159	.669	2.687	1.789	...	...
"Banner" bone flour	.065	.091	23.990	1.160	...	...	14.940	14.940	...
Blood, swine	1.040	1.370	.031	.028	.647	1.200	.280	.076	.204
"Black albumen"	.027	1.247	.039	.011	.820	1.550	.122	.037	.085

From the work of Vorbrodt (1910) we quote the table on the following page setting forth a separation of general groups of phosphorus compounds.

Rengniez (1911) reports most of the phosphorus of flour to be in the forms of phytin and nuclein. The highest phosphorus content was found in flour made from the germs. Wheat germ flour showed 2.9 percent total phosphoric acid, of which 2.17 percent was in the form of phytin and 0.70 percent in the form of nuclein.

CONTENT OF DIFFERENT FORMS OF PHOSPHORIC ACID IN SEEDS
Vorbrodt, (1910)

Seeds of	Total P_2O_5	Mineral P_2O_5		Soluble organic P_2O_5		Protein P_2O_5		Lecithin P_2O_5	
	Percent	Percent of seed	Percent of total	Percent of seed	Percent of total	Percent of seed	Percent of total	Percent of seed	Percent of total
Indian corn (*Zea Mays*)...	0.814	0.050	6.14	0.398	48.90	0.319	39.18	0.047	5.77
Wheat (*Triticum sativum*)	1.04	0.134	12.88	0.311	29.90	0.567	54.51	0.028	2.69
Barley (*Hordeum distich.*) I	1.07	0.15	14.02	0.389	36.36	0.531	49.63	.....	....
" " II	0.83	0.127	15.30	0.285	34.34	0.388	46.75	0.030	3.61
Rye (*Secale cereale*).....	0.98	0.302	30.82	0.283	28.88	0.382	38.98	0.013	1.33
Lentil (*Lens esculenta*) II	0.70	0.134	19.14	0.065	9.29	0.435	61.71	0.069	9.86
Windsor bean (*Vicia faba minor*).....	1.07	0.081	7.57	0.047	4.39	0.894	83.56	0.048	4.49
Rape (*Brassica napus oleifera*).....	1.23	0.102	8.29	0.468	38.05	0.66	53.66	.....	....
Hemp (*Cannabis sativa*)..	1.74	0.213	12.24	0.261	15.00	1.266	72.76	.....	....
Spruce (*Picea excelsa*)....	1.57	0.138	8.70	0.340	21.65	1.092	69.56	0.029	1.85
Pine (*Pinus cembra*).....	1.07	0.079	7.38	0.154	14.39	0.837	78.22	0.053	4.95

General phosphorus separations are also quoted from the work of Rising (1910).

PHOSPHORUS COMPOUNDS IN PEAS, BEANS AND FLOURS
Rising (1910)

	Moisture	Total phosphorus		Phosphorus of phosphatids		Phosphorus of inorganic phosphates		Phosphorus of phytin		Phos. of nuclein substance and phosphoprotein	
	Percent	Percent of solids found directly	Sum of other determinations	Percent	Percent of total P	Percent	Percent of total P	Percent	Percent of total P	Percent	Percent of total P
Yellow peas....	13.7	0.579	0.565	0.0586	10.1	0.019	3.3	0.110	19	0.378	65.1
Brown beans..	11.8	0.560	0.5167	0.0397	7.	0.019	3.4	0.290	52	0.168	30.
Rye flour.....	11.85	0.313	0.3278	0.0073	2.8	0.090	2.8 [1]	0.0885	25	0.142	45.3
Rice flour.....	13.5	0.1665	0.1891	0.0067	4.	0.0116	7.	0.1144	69	0.0564	33.
Graham flour..	12.4	0.287	0.2400	0.0058	2.	0.0381	13.2	0.0819	29	0.1142	39.

(1) Apparently a misprint for 28.

Hooper (1911) states that unmilled rice contains about 0.65 percent P_2O_5, while polished rice contains 0.38 percent. The portion of the rice which is removed by the milling process contains 3.36 percent P_2O_5. He reports Indian wheat to contain 0.69 percent P_2O_5, and flour from the same 0.21 percent P_2O_5.

Aron and Hocson (1911a) found in husked rice 0.7-0.8 percent P_2O_5; undermilled rice, 0.45-0.6 percent; and overmilled rice, 0.15-0.35 percent.

Bernardini (1912) gives the distribution of phosphorus in rice as follows:

DISTRIBUTION OF PHOSPHORUS IN RICE (Bernardini, 1912)

P_2O_5 contained in	In embryo, percent	In whole seed, percent
Total	6 20	0 950
Lecithin	0 04	0 003
Lecithid	0 22	0 018
Phytin	5 14	0 436
Mineral part	0 04	trace
Nuclein	0 76	0 502

Adler (1912a, 1912b) investigated the nature of the phosphorus compounds of brewing products. Eighty percent of the phosphorus of beer is inorganic; 20 percent organic. Of the organic phosphorus a part is combined with carbohydrates, and a part with proteins. Lecithin and phytin are not present. Of the phosphates, half are united with alkalis and half with alkaline earths. Wort contains both organic and inorganic phosphorus, and in about the same proportion as in beer. Malt contains alkali and alkaline earth phosphates, as well as phytin. Malt sprouts also contain alkali and alkaline earth phosphates, in greater amounts than either the barley or the malt.

Swanson (1912) reported investigations with regard to the relations between the percentages of acidity and percentages of ash, amino compounds, and total and water-soluble phosphorus of wheat flours, the work being part of a general study on the relation between chemical composition and baking qualities of flour. The total phosphorus varies from 0.093 percent (in second middlings) to 0.373 percent (in ship-duster flour), the amount in wheat being given as 0.482 percent; the water-soluble phosphorus at 25° varies from 0.017 percent (first and second middlings) to 0.114 percent (fifth break); and the water-soluble at 40°, from 0.023 percent (first middlings) to 0.191 percent (ship-duster flour), that of wheat being 0.218 percent.

ORGANIC AND INORGANIC PHOSPHORUS IN FOODS

Methods for the estimation of inorganic phosphorus as distinct from organic phosphorus in foods are not yet sufficiently well established to warrant the placing of emphasis upon minor differences in results obtained. One of us (E. B. F.) in collaboration with Lehmann, Collison and Whittier published methods for this estimation in both plant and animal tissues (Ohio Agr. Exp. Sta. Bul. 215), and results obtained by these methods are submitted in the tables on pp. 77 and 78. In later studies of these methods the one used for

animal tissues has promised well, while the outcome of further work with the method for vegetable products seems problematical. Certain general conclusions, however, we feel it safe to draw from these data. Thus, all of the parts of plants contain inorganic as well as organic phosphorus. The proportion of the total phosphorus which is inorganic is, in general, much higher in leaves, stems, fruits and roots than in seeds. Among the cereal products the proportion of inorganic phosphorus in the total is much higher in brewer's grains and malt sprouts than in others.

Organic and inorganic phosphorus in meat and milk are somewhat nearly equally divided. Inorganic phosphorus predominates in whey, while eggs are practically free from inorganic phosphorus.

Since the whole matter of inorganic phosphorus estimation in vegetable substances is in an unsettled state we have made no effort to present all the data available. Below are references to a few of the investigations which report inorganic phosphorus estimations in vegetable substances:

Zaleski (1902, 1907); Schlagdenhauffen and Reeb (1902); Hart and Andrews (1903); Schulze and Castoro (1904); Suzuki and Yoshimura (1907); Suzuki, Yoshimura and Takaishi (1907); Stutzer (1908); Heubner and Reeb (1908); Forbes, Lehmann, Collison and Whittier (1910); Forbes, Whittier and Collison (1910); Hart and Tottingham (1910); Hartwell and Quantz (1910); Rising (1910); Vorbrodt (1910); Hartwell and Hammett (1911); J. W. Ames and Boltz (1912); Hartwell (1913).

PHYTIN IN FOODS

Posternak (1903a, 1903b, 1905) found phytin in the aleurone grains of red fir, hemp and sunflower, in peas, lentils, white kidney beans, rape, lupine, wheat, corn, potatoes, dahlia bulbs, carrots and even onions, and says that in grains, where there is little mineral phosphate, it forms at least 70-90 percent of the total phosphorus. He looks upon it as a storage of reserve material for the development of the embryo. The following table is taken from the reports of 1903.

PHYTIN AND LECITHIN PHOSPHORUS IN FOODS (Posternak, 1903)

	Total phosphorus, per cent	Phosphorus of phytin, per cent	Phosphorus of phytin, in per cent of total phosphorus	Phosphorus of lecithin, in percent of total phosphorus
Red fir	0 656	0.600	91.46	1.1
Hempseed (cortex removed)	1.460	1.330	91 44	3.1
Sunflower seed (cortex removed)	0.830	0.723	86.26	1.8
Peas	0.367	0.260	70.80	6.2
Lentils	0.299	0.247	82.60	6.7
White kidney beans	0.512	0.418	81.60	6.0

Gilbert and Posternak (1905) say that in a mixed diet the main part of the phosphorus is in the form of phytin. It is now well-known that phytin as estimated by Gilbert and Posternak includes compounds other than phytin.

Suzuki, Yoshimura and Takaishi (Suzuki and Yoshimura, 1907; Suzuki, Yoshimura and Takaishi, 1907), from their studies of the distribution of phytin, report the following determinations of the forms of phosphorus in bran, seeds, seedlings and a few other substances.

PARTITION OF THE PHOSPHORUS COMPOUNDS OF FOODS (Suzuki, Yoshimura and Takaishi)—Percent

Material examined	Total phosphorus	Phosphorus in lecithin		Phosphorus soluble in 0.2 percent HCl		Of that soluble in 0.2 percent HCl			
						Inorganic		Organic	
	In dry substance	In dry substance	Percent of total	In dry substance	Percent of total	In dry substance	Percent of total	In dry substance	Percent of total
Rice bran	2 27	0.02	0.86	1.92	84.48	0.13	5.89	1.68	74.17
Wheat bran	1.114	0.010	0.81	0.638	57.24	0.050	4.49	0.579	52.00
Seeds of sesame (*Sesamum indicum*)	0.772	0.030	3.91	0.144	18.61	trace	trace	0.125	16.24
Seeds of castor bean (*Ricinus communis*)	0.261	0.013	5.13	0.110	42.29	"	"	0.109	41.61
Oil cake, rape (*Brassica napus*)	1.195	0.034	2.88	0.592	49.52	"	"	0.532	44.46
Barley bran (*Hordeum vulgare*)	0.541	0.010	1.85	0.327	60.44	0.089	16.45	0.238	44.00
Millet bran (*Panicum frumentaceum*)	0.765	0.026	3.40	0.363	47.45	trace	trace	0.344	44.97
Rice seed	.....	.....	1.47	...	44.28	....	"	....	41.64
" seedlings	.....	... .	4.10	....	76.00	....	25.22	....	42.52
Rape seed	.....	.....	6.95		64.51	....	trace	....	62.11
" seedlings	.....	.....	9.83	....	78.18	....	70.02	....	2.88
Barley seed	.....	.....	4.14	....	58.62	..	trace	....	56.55
" seedlings	.....	.....	8.05	....	73.34	....	65.98	....	6.89
Wheat seed	.. . .	.....	3.32	....	56.56	....	trace	....	55.50
" seedlings	.....	.....	6.97	....	74.26	....	63.27	....	10.72
Steamed bone meal (air-dry)	10.077	0.009	0.09	10.066	99.89	8.919	88.51	0.267	2.65
Fresh bones of young cock (1 percent HCl used)	9.186	.....	....	7.168	78.03	6.514	70.91	0.167	1.82

The authors conclude:

"1. The greater part of the phosphorus of plant seeds consists of the organic compound soluble in water and dilute mineral acids which has been obtained by Schulze, Palladin, Winterstein, Posternak, Patten and others, and named 'Anhydro-oxy-methylen-diphosphoric acid' or 'Phytin.'

"From rice bran we have isolated about 8 percent and from wheat bran about 2 percent phytin.

"2. But in roots, bulbs and fruits inorganically combined phosphoric acid predominates.

"3. The occurrence of phytin in bones is doubtful.

"4. During the germination of plant seeds, either in the light or in the dark, the inorganically combined phosphoric acid increases notably.

"Also if one grinds rice or wheat bran or different seeds and lets them stand suspended in water for some days, phosphoric acid forms in considerable quantity at the expense of phytin.

"5. An enzyme was isolated from rice and wheat bran that splits phytin into phosphoric acid and inosite. It is apparently a new enzyme and seems to be widely distributed in the plant world."

Hart and Tottingham (1910) proved the presence of such a compound also in the grains of corn, oats and barley, and distributed throughout the entire seed, in these cereals, more than in wheat. Below is their description of the separation of parts of the seeds.

"In the wheat kernel phytic acid as a salt exists largely in the outer aleurone layers and consequently is found in very large proportion in wheat bran. In order to determine whether similar distribution obtained in the corn kernel this seed was mechanically divided into three parts—the outer layer or corn bran (pericarp), the germ, and the starch and gluten cells (endosperm)." The determinations below are stated on an air-dry basis.

	Total P Percent	P soluble in 0.2 percent HCl Percent
Entire seed	0.29	0.13
Corn bran	0.13	0.00
Corn germ	0.38	0.13
Corn gluten	0.42	0.15

"It is clear from these data that in the maize grain, phytin is not localized in the outer layers.....In this instance there appears to be none in the outer skin or seed coats, while there is, on the contrary, more or less uniform distribution throughout the entire seed."

The oat "seed was mechanically separated into the hull or bran layers (pericarp) and kernel. The former is fibrous and forms a considerable part of the grain. The latter consists of the aleurone layer and starch cells (endosperm) and the embryo."

	Total P Percent	P soluble in 0.2 percent HCl Percent
Entire seed	0.41	0.18
Oat kernel	0.41	0.22
Oat hull	0.41	0.09

"It is apparent from the data that while the seed coats carry a total amount of phosphorus comparable with the other parts of the grain, the proportion of phytin in the outer layers is relatively small. On the other hand it constitutes 50 percent of the total phosphorus bearing bodies of the remaining parts of the seed."

Of barley "the separation of the entire seed into the outer fibrous coats (pericarp), here designated as bran, and into the aleurone layer, starch cells and embryo (kernel) was carried out mechanically."

	Total P Percent	P soluble in 0.2 percent HCl Percent
Entire seed	0.50	0.19
Bran, or hull	0.22	0.15
Kernel, or germ	0.57	0.17

"These results make it manifest that phytin is not concentrated in the outer seed coats, although it does constitute a very large proportion of the total phosphorus existing there. Phytin appears to be distributed throughout the entire seed."

Vorbrodt (1910), after studying the distribution of the kinds of phosphorus compounds in maize seed, says: "In corn seeds almost nine-tenths of the total phosphoric acid and almost all of that of the soluble organic compounds is in the germ and the scutellum. In the germ and scutellum there are large amounts of nucleoproteins, while the rest of the seed contains but little of them."

See also Rising p. 79, and Rengniez p. 78, Bernardini p. 79-80.

DISTRIBUTION OF LECITHIN IN PLANTS AND IN MISCELLANEOUS FOODS

The data of the table below are taken from Schulze and Steiger (1889), Schulze and Frankfurt (1894), and Schulze (1897, 1908b). Phosphorus determinations were made on the ether-absolute alcohol extract and these values were interpreted as lecithin (3.84 percent P). The values, therefore, must not be taken as the absolute content, but they show, rather, the relative amounts of phosphorus in such a combination. Where determinations have been found to differ in the reports of different years, that given latest has been taken, and the dates are recorded in all cases.

PHOSPHATID PHOSPHORUS IN VEGETABLE SUBSTANCES—Percent, Dry Basis

Substance Seeds of	Date	Phosphorus in ether-alcohol extract	Ether-alcohol soluble phosphorus computed to lecithin	Total phosphorus	Phosphatid phosphorus in percent of total
Yellow lupine (*Lupinus luteus*)	1908	0.082	2.14		
Blue " (" *angustifolius*)	"	0.084	2.19	1.53	5.5
Vetch (*Vicia sativa*)	1897		1.09		
" (*Faba vulgaris*)	1889	0.031	0.81		
Soy bean (*Soja hispida*)	1889	0.063	1.64		
Peas (*Pisum sativum*)	1897		1.05		
Garden beans	1908	0.049	1.27	1.32	3.7
Kidney beans (*Phaseolus vulgaris*)	"	0.035	0.90		
Lentil (*Ervum lens*)	1897		1.03		
Wheat (*Triticum vulgare*)	"		0.43		
Barley (*Hordeum distichum*)	"		0.47		
Maize (*Zea mays*)	"		0.25		
Rye	1894	0.022	0.57		
Buckwheat (*Polygonum fagopyrum*)	1897		0.53		
Flax (*Linum usitatissimum*)	"		0.73		
Hemp (*Cannabis sativa*)	"		0.85		
Sunflower	1908	0.017	0.44		
Cucumber (*Cucurbita pepo*)	"	0.021	0.55	2.10	1.0
Poppy (*P. somnif.*)	1894	0.009	0.25		
Castor-oil plant (*Ricinus*)	1908	0.011	0.29	1.14	1.0
Beech (*Fagus*)	"	0.011	0.30		
Chestnut (*Castenea vesca*)	"	0.026	0.67		
Horsechestnut (*Aesculus hippocastanum*)	"	0.026	0.67		
Pine (*Pinus silvestris*)	1897		0.49		
Red pine (*Picea excelsa*)	"		0.27		
White pine (*Abies pectinea*)	"		0.11		
Siberian stone-pine (*Pinus cimbra*)	1908	0.038	0.99	1.16	3.2
Cluster Pine (*Pinus maritima*)	"	0.033	0.86	2.60	1.3
Wheat germ	1894	0.059	1.55		
" bran	"	0.020	0.54		
Sesame cake I	"	0.021	0.56		
" " II	"	0.019	0.50		
" " III	"	0.006	0.15		
Oil cake (flax) I	"	0.004	0.10		
" " " II	"	0.009	0.25		
Peanut cake I	"	0.014	0.37		
" " II	"	0.001	0.04		
Coconut cake	"	0.007	0.19		
Palm cake	"	0.009	0.22		
Hemp cake	"	0.025	0.69		
Beechnut cake	"	0.006	0.17		
Leafbuds of pears	"	0.020	0.54		
" " hazel	"	0.028	0.77		
" " maple	"	0.024	0.65		
Young grass	"	0.016	0.45		
" vetches	"	0.039	0.86		
Mushroom (*Agaricus campestris*)	"	0.012	0.32		
" (*Boletus edulis*)	"	0.073	1.94		

From the work of Stoklasa (1896a, 1896b) we quote the following summary of conclusions as to the distribution of lecithins:

"1. **Roots.** Annual plants contain very little lecithin in their roots, the maximum being 0.3 percent; at completion of growth this falls to 0.1 percent. Perennials or biennials contain a larger quantity at the close of the season, this serving as a reserve for use in building new cells.

"2. **Stalk.** Stems contain 0.3 to 0.4 percent lecithin; after the fruit ripens this decreases rapidly, being at most 0.1 percent then for annuals.

"3. **Leaves.** A considerable quantity of lecithin is continually present in the leaves; it begins to disappear after fertilization and during fruit formation, if at the same time the leaves begin to turn yellow. Pure leaf substance is the richest part of the plant in lecithin, except the anthers and pollen grains at the time of blooming. Leaves contain up to 40 percent of their total phosphorus as lecithin. Since I have observed that the removal and destruction of lecithin and chlorophyl-coloring matter run parallel, and since I consider it most probable that this coloring matter contains a quantity of phosphorus corresponding to that of lecithin, I am of the opinion that chlorophyl itself is a lecithin.

"4. **Flowers.** The petals, it appears, contain the most lecithin at the stage of fullest development of the buds; after fertilization the lecithin decreases. The male organs, pollen filaments, anthers and pollen grains, are the parts richest in lecithin. The pollen grains, containing almost 6 percent of lecithin, are the richest of all. This corresponds to the fact that the sperm of higher animals is especially rich in lecithin."

From the work of Stellwaag (1890) we quote the following estimations of lecithin in the ether and benzene extracts of miscellaneous vegetable foods.

LECITHIN AND PHOSPHORUS IN ETHER EXTRACT AND BENZENE EXTRACT OF FODDERS—Percent (Stellwaag, 1890)

Fat of	Ether Extract		Benzene Extract	
	Lecithin	Phosphorus	Lecithin	Phosphorus
Hay	Traces	Traces	...	...
Peas	27.37	1.049	6.95	0.247
Vetch	22.94	0.881	7.65	0.26
Tick bean	21.29	0.818	4.11	0.14
Lupine blossom	4.59	0.172	...	...
Buckwheat	1.88	0.072	2.53	0.083
Soja bean	1.26	0.066	1.57	0.063
Cabbage	6.99	0.268	3.27	0.123
Poppyseed cake	13.27	0.40	6.24	0.222
Cottonseed cake	4.35	0.166	1.52	0.058
Potatoes	3.07	0.117	...	...
Barley	4.25	0.163	2.37	0.091

Von Bitto (1894) prefers a methyl alcohol extraction (20 extractions) to the method of Schulze and Steiger, for phosphatid determination, and reports the following amounts found in that way:

LECITHIN PHOSPHORUS AND LECITHIN IN VARIOUS SEEDS—Percent Dry Basis

	P	Lecithin
Paprika	0.0687	1 788
Vicia sativa (vetch)	0.0621	1.618
Lupinus luteus (yellow lupine)	0.0746	1.933
Soy beans	0.0750	1.955
Wheat	0.0222	0.578
Rye	0.0256	0.667
Barley	0.0227	0.592
Yellow maize	0.0185	0.482

Schulze (1895) supports his method in comparison with that of von Bitto.

Th. Dietrich (1902) reports 1.48 to 1.89 percent of lecithin in the dry substance of brewer's grains.

Stoklasa (1895) found in sugar beet leaves 1.12 percent, and in the root 0.43 percent lecithin, on the dry basis.

W. Koch (1905a) reported lecithin estimations on a number of common foods, as below:

LECITHIN IN SOME COMMON FOODS (W. Koch, 1905)

	Gm. lecithin
1 lb. calf brain	20-25
1 lb. shad roe	18-20
12 eggs	12-16
1 lb. calf liver	12-15
1 lb. sweetbreads	12-15
1 lb. lamb fries	10-12
1 lb. meat (beef)	5-7
1 lb. peas or beans	5-7
1 lb. salmon	5-6
1 lb. bread	0.5-1
1 lb. vegetables	0.3-0.5
1 pint human milk	0.4
1 pint bovine milk	0.3
1 lb. mushrooms	0.2

Heubner and Reeb (1908) made determinations of the amount of phosphorus in the forms of its different compounds in a number of common foods, and their table is given below. Heubner (1911) says later that the method used here is inexact for the estimation of organic phosphorus, for instance, phytic acid.

PHOSPHORIC ACID DISTRIBUTION IN CERTAIN FOODS, Percent
Heubner and Reeb (1908)

Material	Dry substance	In the dry substance (P)						In the fresh substance (P)				
		Total P		As phosphatid	As soluble phosphate	As water-soluble ester	As nuclein and phosphoprotein	Total	As phosphatid	As soluble phosphate	As water-soluble ester	As nuclein and phosphoprotein
		Directly determined	By addition									
Horse flesh	26.0	0.74	0.73	0.15	0.44	0.04	0.10	0.192	0.039	0.114	0.010	0.026
Cow's milk	12.6	0.84	0.80	0.05	0.25	0.05	0.45	0.106	0.006	0.032	0.006	0.057
White of hen's egg	12.6	0.12	0.11	0.00	0.02	0.02	0.07	0.015	0.000	0.003	0.003	0.009
Bread	70.1	0.14	0.13	0.01	0.05	0.00	0.07	0.098	0.007	0.035	0.000	0.049
Rice	87.8	0.11	0.11	0.005	0.005	...	0.10	0.097	0.004	0.004	...	0.088
Bran	98.8	1.47	1.29	0.02	0.25	0.35	0.67	1.452	0.020	0.247	0.346	0.662
Turnips	13.6	0.40	0.38	0.03	0.20	0.11	0.04	0.054	0.004	0.027	0.015	0.005
Sugar beets	14.6	0.19	0.19	0.04	0.08	0.05	0.02	0.028	0.006	0.012	0.007	0.003
Green cabbage	12.3	0.48	...	0.07	0.22	(0.09)	0.10	0.058	0.009	0.027	(0.011)	0.012
White cabbage	8.3	0.31	...	0.06	0.14	(0.07)	0.04	0.026	0.005	0.012	(0.006)	0.003

Vageler (1909) finds, as do others, that seeds contain but a small amount of inorganic phosphorus; also that the largest amount of phosphatid is to be found in a plant at the time of its fullest vegetation and while the seeds are forming; when autumn comes and the seeds have ripened and leaves are withering, the easily soluble phosphorus is low; also that the phosphorus content of a normal, healthy plant is greater than that of an ill-nourished plant. Vageler also questions whether it may not be that the low values that observers have found for the phosphorus content of the ether-alcohol extract of dried vegetable products is due to a partial breaking up of phosphatid during the drying process.

ANALYSES OF FRESH AND DRIED VEGETABLE TISSUE FOR WATER AND PHOSPHATID PHOSPHORUS (Vageler, 1909)—Percent

Substance examined	Fresh material		Dried material	
	Water	Phosphatid phosphorus	Water	Phosphatid phosphorus
Lettuce	94.93	0.1487	10.37	0.0731
Spirogyra	89.74	0.0376	9.596	0.0353
Rhubarb leaves	90.165	0.2934	7.218	0.0578
Grass	85.55	0.0780	4.898	0.584
Hay	14.74	0.0169	12.98	0.0091
Lupine seeds	17.26	0.0496	8.03	0.0398
Oat grains	14.94	0.0203	11.66	0.0189

Winterstein and Smolenski (1909) find that the phosphatid obtained from wheat flour is a mixture of at least three phosphatids with cholesterin and other substances; and K. Smolenski (1909) isolated two phosphatids from wheat germ.

LeClerc and Wahl (1909) report finding considerable loss of phosphoric acid and of other ash constituents in the change from barley to malt. At the same time there was an increase of alcohol-ether soluble phosphorus, and probably a part of the other forms of organic phosphorus are transformed to phosphatids, while considerable, as others have found, becomes inorganic. Of the 130 barleys analyzed the general average of total P_2O_5 is 1.04 percent, and of lecithin 0.52 percent in the water-free substance; and of 43 malts the general averages are 1.03 percent total phosphoric acid and 0.75 percent lecithin. The average percent of alterations during malting are computed to a loss of 12.7 percent of the total phosphorus and a gain of 44.3 percent of the lecithin.

Fraps and Rather (1912) have investigated the composition of the ether extract of several kinds of hay, straw and other roughage. The phosphorus content of the ether extract may be considered roughly to indicate the phosphatid content of the products. From

these figures it would appear that the phosphatid content of these species of roughage is low, as indeed all roughage is, and also that peanut hay is distinctly richer in ether-soluble phosphorus than the other kinds of hay studied. Below are figures from this study.

NITROGEN AND PHOSPHORIC ACID OF THE ETHER EXTRACT OF HAYS AND FODDERS (Fraps and Rather, 1912)

Feed	Total ether extract Percent	Percent of extract	
		Nitrogen	Phosphoric acid
Alfalfa hay	1.26	0.23	0.06
Bermuda hay	1.55	0.38	0.08
Buffalo grass hay	1.28	0.33	0.06
Burr clover	2.72	0.44	0.10
Corn shucks	0.61	0.20	0.19
Cowpea hay	3.15	...	0.13
Guam grass	1.78	0.56	0.14
Johnson grass hay	1.29	0.26	0.09
Johnson grass hay	1.38	0.34	0.15
Kafir fodder	1.99	0.39	0.10
Millet	1.53	0.19	0.09
Oat hay	2.12	0.33	0.05
Para grass hay	0.86	0.23	0.25
Peanut hay	8.17	0.07	0.18
Rice straw, Japan	1.47	0.26	0.02
Rice straw, Honduras	1.24	0.18	0.06
Sorghum	1.47	0.23	0.09
Vetch hay	1.59	0.42	0.06

See also Posternak, p. 81, Rising, p. 79, Suzuki, Yoshimura and Takaishi, p. 82, Vorbrodt, p. 79, and Bernardini, p. 79-80.

DISTRIBUTION OF NUCLEIN PHOSPHORUS IN FOODS

There are no well-established methods for the routine estimation of nuclein phosphorus in miscellaneous foods. Nuclein phosphorus has been estimated, however, by various more or less satisfactory methods, and for the results of some of these determinations we would cite the work of Heubner and Reeb (1908), Jebbink (1910) (60 articles of human diet) and Jordan, Hart and Patten (1906).

In Klinkenberg's (1882) study of nucleins he gives us the following as the content of nuclein phosphorus in seed cakes compared with meat residues and with yeast.

NUCLEIN PHOSPHORUS OF SEED CAKES AND MEAT RESIDUES
Klinkenberg (1882)

	Nuclein P Percent
Poppy seed cake	0.0707
Peanut cake	0.0360
Rape seed cake	0.0676
Cotton seed cake	0.0630
Palm cake	0.0344
Residue from meat extract preparation I	0.0307
Residue from meat extract preparation II	0.0530
Yeast	0.198

About 3.5 percent of wheat germ is tritico-nucleic acid, which was first studied by T. B. Osborne and Campbell (1900a), and later by T. B. Osborne and Harris (1902) and Levene and LaForge (1910). This acid is different in its makeup from the animal nucleic acids. Osborne and Campbell isolated the acid itself and also obtained combinations of it with leucosin, a globulin and two proteoses, as well as showing that some of it was left in combination with other insoluble substances. With regard to the combinations in the wheat embryo, however, it is said finally: "That the wheat embryo in fact contained the same nucleic acid *compounds* as we have obtained from the extracts is highly improbable. All that we can conclude is that the embryo contains the different protein substances described, together with nucleic acid, and that these may unite to form a number of different compounds according to the conditions which prevail at any given time."

Funatsu (1907) also estimated nuclein phosphorus in oil cakes. The following data are submitted:

DETERMINATIONS OF THE PHOSPHORUS PARTITION IN PRESS CAKES (Funatsu, 1907)

	Total P_2O_5	Lecithin P_2O_5		Nuclein P_2O_5		P_2O_5 soluble in dilute HCl	
		Percent	Percent of total	Percent	Percent of total	Percent	Percent of total
Soybean cake	1.38	0.17	12.4	0.23	16.5	0.98	71.0
Cottonseed cake	2.25	0 12	5.0	0 30	13.2	1.80	81.7
Rape cake	2.82	0.20	7.0	0.26	9.0	2.37	84.0

See also Rising p. 79, Rengniez p. 78 and Bernardini p. 79-80.

PYROPHOSPHORIC ACID IN VEGETABLE SUBSTANCES

The question of the presence of pyrophosphoric and metaphosphoric acids in cottonseed meal, first raised by Hardin (1892), has called forth investigation, especially because Crawford (1910) thought that he had evidence that the poisonous effects sometimes observed as a result of feeding cottonseed meal to cattle and hogs is due to the presence in the meal of a salt, either organic or inorganic, of pyrophosphoric acid. The evidence of the presence of these acids is in qualitative reactions in extracts of cottonseed meal, which resemble those of the acids in question, and in toxic effects of the meal, or extracts from it, which are similar to those of the acids. More recently, however, both Rather (1912) and Anderson (1912c) have independently shown that all of the reactions in question are given by organic phosphorus compounds, salts of which

they have isolated from cottonseed meal. Both find the acids of the salts isolated to be inosite phosphoric acid (Rather 1913b, Anderson 1914a). It is not markedly toxic in small doses.Withers and Ray (1913) have shown that the only fraction of cottonseed meal which is toxic to rabbits in the amounts used in feeding is that which is not soluble in water or dissolved by digestion with pepsin and pancreatin (one day each), and that if this fraction contains any pyrophosphoric acid it is a non-toxic amount. It is to be concluded that probably there is no pyrophosphoric acid in this meal; also that the principal phosphorus compound present is organic, and of the nature of phytin.

PROPRIETARY PREPARATIONS

Phosphorus compounds as constituents of medicinal preparations have occupied a prominence out of proportion to their usefulness in this relation. While they are of undoubted value as simple nutrients, the idea of their possession of a stimulating function by reason of direct contribution to the nervous tissues, or by reason of other specific effects, has been very greatly overworked. It is true, however, that there is at hand evidence that certain of the organic compounds of phosphorus, lecithin especially, may, in certain pathological conditions, have a curative value; but even in these cases there is need of further experimental work to differentiate between the effects of these compounds in the uncombined state, and the effects of the related compounds as they exist in natural foods. We put no emphasis, therefore, on the usefulness of proprietary medicinal preparations as affected by their phosphorus compounds, but merely enumerate those which have come to our attention, with brief notes as to their general character.

Springer (1894, 1902) prepared a cereal decoction which he recommends to be used with the diet, especially in cases of retarded growth. It is prepared by boiling a mixture of wheat, barley, oats, rye, maize and bran in water and straining out the residues.

Mouneyrat (1902a, 1902b) prepared what he called "Histogénol," a combination of methyl arsenate of sodium and the nucleic acid from herring milt.

Among casein preparations are "Plasmon" (E. Bloch, 1900; Poda and Prausnitz, 1900; Micko, 1900) and "Nutrose," impure sodium salts of casein, "Eucasein," an ammonium salt described by Salkowski (1896b), "Sanose," 80 percent casein and 20 percent albumose (Schreiber and Waldvogel, 1897), and "Sanatogen," sodium-casein glycerophosphate (Snowman, 1905; Gumpert, 1905).

Special glycerophosphate and lecithin preparations are discussed by Frey (1906), especially Baraba's "Nervinol."

Laves (1900) describes "Roborat," a cereal preparation said to contain an abundance of lecithin, and Heim (1904) describes "Bioson" as a protein-iron-lecithin compound containing 1.27 percent lecithin.

Schröder (1905, 1906) describes "Bioplastin," a lecithin preparation, "Histogénol," and "Caudol," a dry malt extract containing phosphates.

"Fersan," prepared from the blood of cattle, contains iron and phosphorus organically combined (Kornauth and Czadek, 1900; Kornauth, 1901).

"Protylin" is a synthetic paranuclein containing about 2.7 percent phosphorus (Kornfeld, 1904; Laguesse, 1905; Fjodoroff, 1907).

EFFECTS OF WATER ON THE COMPOSITION OF FORAGE PLANTS

Kellner, Köhler and Barnstein (1894, 1895) give data which show that both hay and straw were low in the phosphoric acid content of the ash after the dry summer of 1893; and the following figures from von Seelhorst, Georgs and Fahrenholtz (1900) show a like effect in clover and grass, with moisture controlled by irrigation.

PHOSPHORIC ACID CONTENT OF CLOVER AND HAY AS AFFECTED BY THE AMOUNT OF MOISTURE SUPPLIED (Von Seelhorst et al., 1900)

Percent Phosphoric Acid

Water	Plot manured	Plot not manured	
Little	0.456	0.428	Clover
Average	0.536	0.553	"
Much	0.540	0.523	"
Little	0.725	0.660	Meadow fescue
Average	0.597	0.644	"
Much	0.666	0.650	"

Forbes, Whittier and Collison (1910) showed in experiments with oats, grown with various amounts of water, that there is a relation between the phosphorus content of the plant and the water available during growth. The numerical data are below:

ANALYSES OF OAT PLANTS GROWN WITH DIFFERENT AMOUNTS OF WATER—Dry Matter Basis—Percent

Lot	Total water applied to each pot C. C.	Moisture in plant Percent	Ash in dry substance Percent	Phosphorus in dry substance Percent	Calcium in dry substance Percent
Planted Oct. 7, 1908; cut Nov. 20, 1908					
1	1675	86.11	16.77	.884	.526
2	2420	88.51	15.38	.898	.451
3	3165	88.20	15.12	.966	.461
4	3910	87.77	14.72	.979	.515
5	4655	88.06	13.96	.892	.453
Planted Dec. 13, 1909; cut Feb. 26, 1910					
6	1800	83.78	15.17	.647	.440
7	3100	84.57	15.17	.666	.409
8	4400	86.79	15.65	.805	.498
9	5700	87 28	16.02	.787	.463
10	7000	87.75	16.20	.855	.463
Planted Dec. 13, 1909; cut Mar. 7, 1910					
11	2400	79.68	15.37	.684	.461
12	4000	82.44	16.19	.768	.504
13	5600	85.94	16.20	.801	.495
14	7200	85.18	16.18	.818	.488
15	8800	84.76	15.98	.809	.480
Planted Apr. 4, 1910; cut May 11, 1910					
16	900	88.97	18.47	1.12	.542
17	1425	89.59	18 68	1.16	.539
18	2000	89.95	18.54	1.20	.554
19	2625	90.50	18 20	1.22	.493
20	3300	90.73	18.05	1.27	.551

A similar relationship between water and phosphorus was shown by these same authors in forage plants grown in arid regions with and without irrigation. The data are below:

EFFECTS OF IRRIGATION ON MINERAL CONSTITUENTS OF GRASSES Dry Matter Basis—Percent

No.	Ash	Nitrogen	Calcium	Potassium	Phosphorus	Source of sample
1	8.62	2.32	1.67	1.80	.175	Alfalfa; Fallon, Nev.; not irrigated for five years; water table 8 ft. below surface of field.
2	10.34	2.50	1.27	2.38	.220	Alfalfa; Fallon, Nev.; irrigated frequently.
3	16.38	.845	.342	.99	.099	Blue-joint (*Elymus*) ; Fallon, Nev.; sample from dry soil.
4	9.47	766	.250	1.06	.133	Blue-joint (*Elymus*); Fallon, Nev.; sample from land continuously wet by seepage from irrigation ditch.
5	9.78	.895	.410	.92	092	Indian bunch-grass, (*Eriocoma cuspidata*) Fallon, Nev.; sample from dry soil; annual rain-fall less than three inches.
6	16.10	.734	.462	.67	.103	Indian bunch-grass, (*Eriocoma cuspidata*) Fallon, Nev.; sample from land constantly wet by seepage from irrigation ditch.
7	12.11	1.89	1.00	2.14	.142	Bermuda grass. Yuma, Ariz. Not irrigated.
8	11.46	1.39	.709	1.55	.243	Bermuda grass. Yuma, Ariz. Irrigated frequently.

EFFECTS OF FERTILIZERS ON THE COMPOSITION OF FOODS

Since some of the phosphorus compounds of plants are readily soluble in the water which falls upon them as rain, and since we do not know that the salts absorbed by the fertilized plants are the same and therefore have the same solubility as those absorbed by the unfertilized plants, we have no assurance that samples collected from plants which have been grown out-of-doors fairly represent the effects of the fertilizers on the phosphorus compounds of the plants. In the interpretation of numerical data on this matter, therefore, it would seem wise to make liberal allowance for experimental error. It seems altogether probable that the apparent inconsistencies in results which have been obtained are due in part to the factors above suggested. From the mass of material available we select but a small portion.

From the work of Chavan (1908) we quote the following figures showing direct effects of fertilizers on the composition of grass.

INFLUENCE OF PHOSPHORUS AND POTASSIUM IN FERTILIZERS ON THE COMPOSITION OF GRASSES (Chavan, 1908)

Percent—Dry Basis

Fertilizer applied	Protein	P_2O_5	K_2O	CaO	Ash
None	10.29	0.25	1.41	1.52	6.47
P	8.90	0.56	1 80	1.20	6.05
K	11.06	0.24	2.56	1.10	6.82
P, K	10.25	0.57	2.61	0.89	7.21

Parrozzani (1908) states that increasing the inorganic phosphorus available to maize increases the lecithin and phytin phosphorus, but does not affect nuclein phosphorus nor total nitrogen, though protein nitrogen increases slightly and amid-nitrogen decreases correspondingly.

Forbes, Whittier and Collison (1910) made analyses of 24 samples of Kentucky blue-grass taken in 1910 from a variety of types of soil in Ohio and Kentucky, the conditions of taking the samples and the age of the plants being as nearly alike as possible. The range of phosphorus content is from 0.164 to 0.403 percent P in the dry matter. Samples taken the two previous years were all within the same range. The inorganic phosphorus in 17 of the samples ranged from 0.064 to 0. 267 percent, and the organic, from 0.064 to 0.154 percent of the dry matter. Blue-grass from experiment plots differently fertilized gave results as in the table below.

Potassium chloride appears to have increased the organic phosphorus of the grass. The effects of the fertilizers are generally direct and consistent.

ANALYSES OF BLUE-GRASS DIFFERENTLY FERTILIZED
Forbes, et al. (1910) Percent of Dry Matter

No.	Ash	Nitrogen	Calcium	Potassium	Phosphorus	Inorganic phosphorus	Organic phosphorus	Source of Sample
1	5.48	1.49	.230	1.83	.277	.176	.101	Wooster, O. Station lawn. Fertilized with sodium phosphate.
2	5.08	1.52	.247	1.58	.235	.135	.100	Wooster, O. Station lawn. No fertilizer.
3	5.47	1.50	.222	1.86	.265	1.38	127	Wooster, O. Station lawn. Fertilized with potassium chloride.
4	5.01	1.46	.311	1.63	.236	.130	.106	Wooster, O. Station lawn. Fertilized with lime (calcium oxide).
5	6.16	1.48	.250	1.82	.264	.161	.103	Fertilized with sodium phosphate, potassium chloride and lime (calcium oxide).

Lewoniewska (1911) reports observations on the phosphorus content of oats (grain) as affected by the soil. Protein and lecithin phosphorus varied little, but both phytin and phosphates varied much. With variation in the phosphorus of the soil the relation of total phosphoric acid to nitrogen varied between 100:50 and 100:32, while the relation of phosphorus compounds soluble in 1 per cent acetic acid varied between 100:20 and 100:6.

From the reports of Ames and his associates (J. W. Ames, 1910; J. W. Ames, Boltz and Stenius, 1912) with regard to the effects of fertilizers on the phosphorus content of wheat we quote several tables:

EFFECT OF SEASON AND PLANT FOOD SUPPLIES ON THE PHOSPHORUS AND NITROGEN CONTENT

Phosphorus content of wheat grain and straw—Percent

Treatment	1904		1907		1908		Maximum variation due to season	
	Grain	Straw	Grain	Straw	Grain	Straw	Grain	Straw
Plot 2, phosphorus	.395	.072	.3839	.0563	.3545	.0364	.0405	.0356
Average of unfertilized plots	.366	.105	.3053	.0548	.3234	.0469	.0607	.0581
Difference due to fertilization	.029	—.033	.0786	.0015	.0311	—.0105	.....	.....

AVERAGE PERCENTAGE OF PHOSPHORUS IN THE WHEAT GRAIN AT WOOSTER

Treatment	Phosphorus in grain
	Percent
Unfertilized	.3143
Nitrogen or potassium without phosphorus	.3080
Phosphorus, without nitrogen	.3690
Phosphorus, with nitrate of soda	.3332
Phosphorus, with organic nitrogen	.3615

AVERAGE PERCENTAGE OF PHOSPHORUS IN THE WHEAT GRAIN AT STRONGSVILLE

Plot treatment	Year and cross dressing			
	1908		1909	
	Floats	Lime	Floats	Lime
Unfertilized	.4059	.3270	.4646	.2947
Nitrogen, in nitrate of soda	.4168	.2837	.4182	.2775
Phosphorus, without nitrogen or potassium	.4449	.4122	.4689	.4116
Phosphorus, with nitrate of soda only	.4572	.3643	.4671	.3845
Phosphorus, potassium and nitrogen	.4287	.4173	.4736	.4522

From the extended studies from which the above figures are taken Ames concludes in part as follows:

"The composition of the wheat crop grown on the unfertilized plots of two soils, containing different amounts of phosphorus, potassium and nitrogen, is in accordance with the composition of these soils.

"The proportion of phosphorus, potassium and nitrogen in the wheat plant is increased by the addition of these elements to the soil.

"Although the extent of variation due to seasonal conditions is greater than that produced by changes in the composition of the soil, the variations due to soil treatment are relatively the same for the different seasons.

"Phosphorus applied to soil, showing a deficiency of this element as measured by crop yields, increases the amount of phosphorus in the grain. Associated with this increased accumulation of phosphorus there is an increased quantity of potassium and a decreased amount of nitrogen.

"The addition of lime to the soil increases the amount of phosphorus assimilated by the wheat plant. With this increase in the phosphorus content there are the same variations in the nitrogen and potassium as are produced by the addition of phosphorus.

"The composition of the wheat crop from plots on the same soil treated with five different carriers of phosphorus, namely: acid phosphate, bone meal, dissolved bone black, basic slag, and barnyard manure, shows that the phosphorus content of the wheat plant has been increased to the greatest extent by manure.

"The application of untreated rock phosphate to a soil well supplied with nitrogen and potassium, increases the phosphorus content of the wheat plant to a marked extent.

"The percentage of nitrogen in the wheat plant varies with the supply at its disposal, and is also influenced to a considerable extent by the supply of phosphorus."

"A comparison of the composition of the wheat plant grown on the same soil, under different conditions of fertilization, gives a better indication of the available supply of nitrogen, phosphorus and potassium in the soil than can be obtained from the analysis of the soil itself."

From a study by J. W. Ames and Boltz (1912) of the effects of fertilizers on the composition of alfalfa we quote the table on the following page. From the study from which these figures were taken, Ames and Boltz conclude in part as follows:

"The phosphorus supply of the soil, as increased by the addition of acid phosphate, is reflected by the phosphorus content of the crop, which follows the same order as the yields obtained.

"When the fertilizer used contained both phosphorus and nitrogen, the increase in the amount of phosphorus over that found in the crop from unfertilized soil is not as great as where phosphorus without nitrogen was applied.

"From 43 to 63 percent of the total phosphorus present in the alfalfa plant is combined as organic phosphorus. There is in each instance, for every condition of fertilization, a greater proportion of the total phosphorus present as organic phosphorus in the second cutting, while the amount of total phosphorus is always larger in the first cutting. The water-soluble phosphorus, which includes practically all the inorganic phosphorus and a considerable portion of that in organic combination, stands in the same order as the total phosphorus and is present in greater amounts in the crop of the first cutting. The quantities of pepsin-insoluble phosphorus which is combined with nitrogen as a highly insoluble compound, and would be of doubtful value from a nutrition standpoint, amounts to about 20 percent of the total phosphorus."

PHOSPHORUS COMPOUNDS OF ALFALFA HAY AS AFFECTED BY COMPOSITION OF FERTILIZER (Ames and Boltz, 1912)

	Fertilizing elements per acre			Lime per acre	Forms of Phosphorus					
	Phosphorus	Potassium	Nitrogen		Total	Organic	Inorganic	Organic Percent of total	Water-soluble Percent of total	Pepsin-insoluble
	Lbs.	Lbs.	Lbs.	Lbs.	Percent	Percent	Percent	Percent	Percent	Percent
First cutting....	Unfertilized			2,500	.2382	.1180	.1201	49.54	80.32	.0560
First cutting....	Unfertilized			5,000	.2734	.1267	.1466	46.35	80.22	.0559
Second cutting..	Unfertilized			2,500	.1885	.1190	.0694	63.13	73.24	.0455
Second cutting..	Unfertilized			5,000	.2106	.1270	.0836	60.31	65.71	.0519
First cutting....	45	..	..	2,500	.3415	.1494	.1921	43.75	83.50	.0947
First cutting....	45	..	..	5,000	.3128	.1513	.1615	48.37	86.48	.0656
Second cutting..	45	..	..	2,500	.2507	.1183	.1324	47.19	79.47	.0550
Second cutting..	45	..	..	5,000	.2447	.1529	.0919	62.49	68.22	.0480
First cutting....	45	25	..	2,500	.3116	.1473	.1643	47.28	85.48	.0619
First cutting....	45	25	..	5,000	.2913	.1295	.1618	44.46	83.92	.0598
Second cutting..	45	25	..	2,500	.2674	.1402	.1272	52.43	73.80	.0475
Second cutting..	45	25	..	5,000	.2184	.1265	.0919	57.92	77.50	.0529
First cutting....	45	25	12	2,500	.2914	.1407	.1507	48.28	78.53	.0640
First cutting....	45	25	12	5,000	.2388	.1169	.1219	48.96	73.17	.0515
Second cutting..	45	25	12	2,500	.2340	.1329	.1011	56.80	70.58	.0445
Second cutting..	45	25	12	5,000	.2316	.1191	.1125	51.43	77.50	.0529
First cutting....	45	..	12	2,500	.2603	.1158	.1445	44.49	.....	.0689
First cutting....	45	..	12	5,000	.2758	.1243	.1515	45.07	85.87	.0508
Second cutting..	45	..	12	2,500	.2423	.1456	.0967	60.10	69.40	.0506
Second cutting..	45	..	12	5,000	.2316	.1344	.0972	58.03	79.46	.0522
*First cutting...	24	56	72	2,500	.2472	.1096	.1376	44.34	.....	.0662
First cutting...	24	56	72	5,000	.2698	.1248	.1450	46.26	.....	.0522
*Second cutting.	24	56	72	2,500	.2184	.1174	.1010	53.75	.....	.0410
Second cutting.	24	56	72	5,000	.2232	.1446	.0786	64.79	.....	.0543

*From 16,000 pounds of stable manure.

Vuaflart (1911, 1912) reports analyses from which it appears that the phosphoric acid variations in flours, from year to year, do not correspond with those of wheats of the same year. He found also that the flour was not as much enriched in phosphoric acid by increased superphosphate treatment as was the grain.

PHOSPHORIC ACID OF WHEAT AND FLOUR

Parts per 100 Parts of Nitrogen (Vuaflart, 1912)

	Wheats			Flours		
	Maximum	Minimum	Mean	Maximum	Minimum	Mean
1908	59.8	49.8	54.5	18.1	14 1	15.3
1909	52.3	42.8	47.5	17.9	12.1	14.4
1910	56.7	37.4	47.4	16.7	11.3	13.7
1911	58.1	44.2	49.9	22.1	12.8	17.9

Swanson (1913) shows that the mineral constituents of flour are much more prominently influenced by the presence or absence of bran than by variations in the ash content of the wheat, the phosphorus content of the flour varying with its grade.

Forbes, Beegle and Mensching (1913) also studied the effects of fertilizers on the phosphorus of the wheat grain. The wheats represented by the following analyses are from the 1911 crop of the 5-year rotation series of the Department of Soils of the Ohio Agr. Exp. Station.

MINERAL ELEMENTS OF WHEATS VARIOUSLY FERTILIZED—Parts per 100 of Dry Substance

Description	Ash	Potassium	Sodium	Calcium	Magnesium	Sulphur	Chlorine	Phosphorus	Inorganic phosphorus	Organic phosphorus
1 Unfertilized	1.87	.523	.122	.051	.153	.243	.089	.403	.0229	.380
2 Phosphorus	1.82	.561	.127	.055	.149	.224	.073	.406	.0219	.384
3 Potassium	1.73	.497	.135	.047	.152	.237	.112	.37	.0192	.351
4 Unfertilized	1.71	.442	.144	.049	.150	.256	.100	.357	.0181	.339
5 Nitrogen	1.73	.467	.147	.055	.154	.253	.096	.349	.0202	.329
6 Nitrogen; phosphorus.	1.75	.467	.139	.057	.149	.243	.085	.358	.0186	.339
7 Unfertilized	1.80	.473	.113	.056	.152	.248	.102	.356	.0208	.335
8 Phosphorus; potassium	1.72	.443	.157	.044	.145	.213	.087	.372	.0179	.354
9 Nitrogen; potassium..	1.61	.465	.136	.043	.139	.258	.100	.337	.0185	.318
10 Unfertilized	1.67	.459	.128	.052	.144	.245	.091	.340	.0179	.322
11 Nitrogen; phosphorus; potassium	1.78	.449	.154	.046	.150	.228	.080	.395	.0207	.374
12 Nitrogen; phosphorus; potassium	1.77	.456	.128	.048	.149	.228	.079	.388	.0176	.370
13 Unfertilized	1.82	.451	.168	.053	.149	.241	.090	.359	.0170	.342

According to Hartwell (1913) the phosphorus content of the purple-top, flat, or strap-leaf turnip (Brassica rapa, L.) is most markedly influenced by the amount of available phosphorus in the soil, so much so that he recommends its use as a means of determining the relative amount of available phosphorus in different soils. Of the range of variation in the specific tests reported he says:—"The percentages of phosphorus in dry matter varied from .27 in turnip roots grown on an extremely deficient soil, to 1.82 in turnips from a soil so abundantly supplied with phosphorus that further manuring even depressed the yield." The inorganic phosphorus (Hartwell and Hammett, 1911) was found to be influenced much more than the total phosphorus. Previously (Hartwell and Quantz, 1910) it had been found that about 70 percent of the phosphorus of this turnip is extractable with 0.2 percent HCl, and mostly precipitable from this extract by molybdate and magnesia mixtures; apparently then, it is present largely as inorganic phosphorus.

Summary. All things considered, we regard the observed effects of soils, fertilizers, and climate upon the phosphorus content of foods, in so far as they are derived from grains, to be without important practical significance. These variations, as a rule, are not large; the food products of greatest value contain but small proportions of the total phosphorus; and neither the farmer nor anyone else is dependent for cereal foods upon the products of any particular farm.

With reference to roughage, however, the case is different; roughage can not be economically transported; it is so bulky. Practically speaking, the farmer is largely dependent on the roughage of his own farm, especially so for green forage. The variations in the phosphorus content of the roughage are large, and these variations as affected by soil, fertilizer and climate constitute factors of first-class practical importance to the breeder of live stock, especially as affecting the growth of bone.

ADDITION OF PHOSPHATES TO SILAGE

An unusual use of a phosphate is reported by Sani (1912). In the proportion of 300 gm. CaH_2PO_4 per quintal of green clover this salt preserved the foodstuff in a silo with much less chemical change and loss than occurred in untreated silage. The temperature of the treated clover did not rise so high as in the untreated silage, and after removal from the silo it was found to be immune to mold. The flowers retained almost their natural color. In 11 months the treated fodder lost 13.7 percent of its weight and the untreated fodder 18.68 percent.

Forbes and Fritz (1914) studied the effects of the ensilage process upon the solubility of rock phosphate (floats). The phosphate was added to the green corn at the time it was put into the silo. The table on the following page sets forth the results.

The increase in total phosphorus during the ensilage process shows that there was a loss of 8.2 percent of dry substance from the untreated corn and 3.5 percent from the phosphated corn.

The increase in water-soluble phosphorus in the untreated corn was not quite equal (7.4 percent) to the arithmetical increase due to the loss of dry matter.

During the ensilage of this untreated corn there was a loss of citrate-soluble phosphorus, in the residue from water extraction, which signifies a process of reversion to less soluble forms.

The one significant increase during the ensilage of the untreated corn was in the inorganic phosphorus soluble in 0.2 percent HCl.

This was much more than enough to account for arithmetical increase from loss of dry substance.

PHOSPHORUS IN SILAGE CORN WITH AND WITHOUT ADDED FLOATS, AND IN SILAGE MADE FROM THE SAME

Percent Water-Free Basis

Product	Total P	Water-soluble P	Citrate-soluble P	Inorganic P soluble in 0.2% HCl	Total water-sol. + citrate-sol. P
Untreated green silage corn	0.200	0.151	0.020	0.086	...
	0.203	0.150	0.021	0.082	...
	0.218	0.147	0.021	0 082	...
Average	0.207	0.149	0.021	0.083	0.170
Silage from untreated corn	0.231	0.159	0.009	0.112	...
	0 228	0.161	0.007	0.110	...
	0.214	0.161	0.009	0.112	...
Average	0.224	0.160	0.008	0.111	0.168
Green silage corn plus floats (250:1)	0 374	0.135	0.055	0.156	...
	0 371	0.138	0.064	0.181	...
	0 367	0.135	0.065	0.178	...
Average	0.371	0.136	0.061	0.172	0.197
Silage from treated corn	0.405	0.158	0.061	0.234	...
	0.387	0.157	0.061	0.243	...
	0.361	0.155	0.059	0 235	...
Average	0.384	0.157	0.060	0.237	0.217

In the phosphated corn there was a loss of water-soluble phosphorus simply through the addition of the floats, that is, the water-soluble phosphorus in the fresh corn was 0.149 percent and in the phosphated corn 0.136 percent, which probably signifies a combination of water-soluble phosphorus of the corn with bases in the floats. This probably took place during the partial drying at 50° C., though perhaps to some extent during the subsequent storage of the sample for nearly a year before the analyses were made.

The water-soluble phosphorus in the phosphated silage was not higher than in the untreated silage. The excess of water-soluble phosphorus in the phosphated silage over the amount in the unensiled, phosphated corn was more than enough to account for the loss in dry matter, but was not as great in amount as in the silage from the untreated corn, again suggesting reversion.

The citrate-soluble phosphorus in the treated fodder and in the silage from the same was naturally higher than in the untreated corn and silage, since a part of the phosphorus of the floats was citrate-soluble. There was no increase in citrate-soluble phosphorus, however, in the residue from the water extraction, during the ensilage of the phosphated corn.

The very considerable increase in inorganic phosphorus soluble in 0.2 percent HCl during the ensilage of the phosphated corn gives us the most significant figure of the test. In the treated corn fodder the inorganic phosphorus soluble in 0.2 percent HCl was 46.4 percent of the total, while in the silage from the same was 61.7 percent of the total.

It is also of interest that the phosphated silage contained more than twice as much inorganic phosphorus soluble in 0.2 percent HCl as the treated silage.

The total phosphorus of the floats was 12.666 percent, the water-soluble phosphorus 0.0129 percent and the phosphorus soluble in 0.2 percent HCl 8.721 percent, all on a water-free basis.

Conclusion. The ensilage of corn will render soluble in 0.2 percent HCl such an amount of the phosphorus of floats, added to corn, as to constitute a practical consideration in the feeding of livestock.

REFERENCES TO EXTENSIVE PRESENTATIONS OF TOTAL PHOSPHORUS CONTENT OF FOODS

Wolff (1871, 1880), König (1903, 1904, 1910), Albu and Neuberg (1906), Schaumann (1910), Sherman (1911).

PART III

THE PHOSPHORUS OF ANIMAL BODIES AND PRODUCTS

GENERAL STUDIES

THE PHOSPHORUS OF GROWN MEN AND ANIMALS

Gilbert and Posternak (1905), in their general discussion of phosphorus therapy from the standpoint of metabolism, sum up the total phosphorus of the human body as being about 30-40 gm. P_2O_5 at birth, and 1600 gm. at middle life. This 1600 gm. is made up of about 1400 in the skeleton, 130 in the muscles, 12 in the brain and nerves, 10 in the liver, 6 in the lungs, about 4 in the blood, etc.

Gilbert and Posternak generalize with regard to the phosphorus distribution in meats in the following way. Meat contains 0.467 percent P_2O_5, and of this 0.274 percent (or 60 percent of the total) is made up of organic compounds.

Lecithin	0.060
Phosphocarnic acid	0.039
Soluble in water but not precipitated by lime	0.039
Nuclein	0.008
Organic phosphorus insoluble in water (other than nuclein)	0.128

The rest is soluble in water and is precipitable by lime, and hence is looked upon as probably inorganic phosphate.

Beaunis has compiled ash analyses of various animal tissues and products, as in the following table, from which one may observe the relative prominence of phosphoric and other oxides in these parts. Approximately half of the ash of bone, muscle, brain and liver is phosphoric anhydrid. In other parts the proportion of phosphorus is much less. Since all of the other elements reported, except sulphur, constitute larger percentages of their oxides than does phosphorus of its oxide, this method of statement exaggerates the actual phosphorus content of these ashes, as compared with the other elements.

BEAUNIS'S COMPILATION OF ASH ANALYSES OF ANIMAL PRODUCTS

Percent of Ash

Tissue	Bone	Calf muscles	Brain	Liver	Lungs	Spleen	Blood	Serum	Blood clot	Lymph	Urine	Milk	Bile	Excrements
Analyst	Heintz	Staffel	Breed	Oidtmann	C. Schmidt	Oidtmann	Verdeil	Weber	Weber	Dahnhardt	Porter	Wildenstein	Rose	Porter
Sodium chloride	....	10.59	4.74	....	13.0	....	58.81	72.88	17.36	74.48	67.26	10.73	27.70	4.63
Potassium chloride	....	....	....	....	....	....	....	....	29.87	....	....	26.33	....	....
Soda	....	2.35	10.69	14 51	19.5	44.33	4.15	12.93	3.55	10 35	1.33	....	36.73	5.07
Potash	....	34.40	34.42	25.23	1.3	9.60	11.97	2.95	22.36	3.25	13.64	21.44	4.80	6.10
Lime	37.58	1.99	0.72	3.61	1.9	7.48	1.76	2.28	2.58	0.97	1.15	18.78	1.43	26.40
Magnesia	1.22	1.45	1.23	0.20	1.9	0.49	1.12	0.27	0.53	0.26	1.34	0.87	0.53	10.54
Ferric oxide	....	....	....	2.74	3.2	7.28	8.37	0.26	10.43	0.05	....	0.10	0.23	2.50
Chlorine	....	....	....	2.58	....	0.54	....	....	.. .	...	....	....	....	....
Fluorine	1.66	....	....	....	....	....	....	....	....	....	....	....	....	....
Phosphoric acid	53.31	48.13	48.17	50.18	48.5	27.10	10.23	1.73	10.64	1.09	11.21	19.00	10.45	36.03
Sulphuric acid	....	....	0.75	0.92	1.4	2.54	1.67	2.10	0.09	....	....	2.64	6.39	....
Carbonic acid	5.47	....	....	....	....	....	1.19	4.40	2.17	8.20	....	....	11.26	....
Silicic acid	....	0.81	0.12	0.27	....	0.17	....	0.20	0.42	0.42	4.06	....	0.36	3.13

From Beaunis, "Physiologie humaine," quoted through Schäfer's "Text-book of Physiology," Vol. I, p. 77.

From Wolff's "Farm Foods," Eng. ed., we quote the following table, from the work of Lawes and Gilbert. The two most important factors determining the percentage of phosphorus in animals is their relative development of skeleton, the tissue richest in phosphorus, and of fat, the tissue poorest in phosphorus. Of the three common meat animals, cattle contain the highest percentage of phosphorus, and swine the lowest percentage of the same.

MINERAL SUBSTANCES OF THE BODIES OF OXEN, SHEEP, AND PIGS
Lawes and Gilbert—Percent, Live Weight

	Ox		Fat calf	Sheep				Fat lamb	Pig	
	Half-fat	Fat		Thin	Half-fat	Fat	Very fat		Thin	Fat
Phosphoric Acid	1.839	1.551	1.535	1.118	1.199	1.040	1.108	1.126	1.066	0.654
Lime	2.111	1.792	1.646	1.321	1.350	1.184	1.240	1.281	1.079	0.636
Magnesia	0.085	0.061	0.079	0.056	0.052	0.048	0.055	0.052	0.053	0.032
Potash	0.205	0.176	0.206	0.173	0.168	0.148	0.158	0.166	0.196	0.138
Soda	0.146	0.126	0.148	0.120	0.104	0.097	0.129	0.103	0.110	0.073
Iron Oxide	0.040	0.024	0.021	0.037	0.042	0.034	0.030	0.026	0.022	0.013
Sulphuric Acid	0.038	0.033	0.041	0.052	0.035	0.031	0.028	0.039	0.053	0.029
Carbonic Acid	0.087	0.071	0.047	0.037	0.053	0.041	0.049	0.043	0.021	0.021
Chlorine	0.059	0.055	0.063	0.072	0.051	0.044	0.066	0.053	0.056	0.043
Silica	0.013	0.006	0.005	0.021	0.020	0.026	0.016	0.012	0.005	0.003

Francis and Trowbridge (1910) have reported phosphorus determinations on the different parts of the carcass of eight beef animals of different ages and in various conditions. Their figures on four animals representing extremes of age or condition are quoted on the following page. Moisture, fat, ash and total phosphorus were determined. The emaciated and the very fat steers contained, in most of the parts, less phosphorus in the dry, fat-free tissue than did the fat calf and the aged cow, the two former perhaps being in more abnormal states of nutrition.

Nerking (1908b) has estimated lecithin in many animal tissues. For data see next page. The high content of nerve tissue in lecithin is notable, the glandular organs contain considerable amounts, and there is evidence that under certain conditions the bone marrow may serve as a storage depot for this important nutrient.

PHOSPHORUS IN THE DIFFERENT PARTS OF THE CARCASS OF BEEF ANIMALS (Francis and Trowbridge, 1910) Percent

	Steer; 1 yr. 10 mos.; emaciated; submaintenance for 11 mos.[1]		Steer; 11 mos.; fat		Steer; 4 yr. 6 mos.; very fat		Cow; 7 yr. 6 mos.; fat	
	Fresh	Moisture and fat free	Fresh	Moisture and fat free	Fresh	Moisture and fat free	Fresh	Moisture and fat free
Blood	0.019	0.116	0.055	0.266	0.021	0.102	0.030	0.153
Hair and hide	0.039	0.101	0.072	0.225	0.048	0.149	0.072	0.222
Circulatory system	0.137	0.801	.....	.....	0.076	1.756	0.103	1 772
Respiratory system	0.159	1.037	0.181	1.181	0.117	0.887	0.164	1.071
Nervous system	0.323	2.305	.....	.....	0.425	2.453	0.354	2.565
Digestive and excretory system	0.183	1.356	0.193	1.204	0.175	0.953	0.140	1.115
Liver	0.333	1.299	0.347	1.339	0.307	1.179	0.339	1.323
Kidney fat	0.067	0.479	0.020	1.470	0.016	1.045	0.016	.....
Offal fat	0.109	0.815	0.034	1.072	0.012	0.710	0.020	.....
Shin, shank, head and tail	0.163	0.762	0.164	0.818	0.142	0.759	0.176	0.899
Round	0.184	0.887	0.191	0.922	0.146	0.842	0.182	0 983
Rump	0.173	0.882	0.143	0.968	0.093	0.892	0.126	1.176
Loin	0.179	0.844	0.158	0.883	0.098	0.872	0.141	1.168
Flank and plate	0.142	0.637	0.125	0.798	0.064	0.732	0.125	1.018
Rib	0.168	0.804	0.149	0.821	0.082	0.804	0.149	1.112
Chuck and neck	0.170	0.824	0.163	0.964	0.123	0.799	0.158	0.923
Composite of leans and fats	0.174	0.799	0.167	0.869	.....	.....	0.153	1.085

(1) "The condition of the skeleton of this steer was remarkable; the marrow having practically disappeared, being replaced with a watery malodorous liquid with none of the properties of normal marrow and totally lacking in greasy or fatty appearances."

LECITHIN DETERMINATIONS IN ANIMAL TISSUES—(Nerking, 1908) Percent, Dry Basis

Organs, etc.	IV Rabbit	V Rabbit	Mean of IV and V Rabbit	VI Cat	VII Hedgehog
Lungs	5.99	5.93	5.96	6.10	4.28
Heart	5.618	6.108	5.863	4.55	10.49
Brain	12.23	12.593	12.41	13.74	22.31
Spinal cord	33.62	36.75	35.19	26.20	18.19
Kidneys	4.30	5 73	5.02	6.26	8.55
Spleen	3.27	5.20	4.24	0.39	6.56
Eyes	3.05	1.32	2.19	....	....
Stomach	2.67	3.94	3.31	....	6.37
Liver	4.22	3.42	3.82	4.99	5.23
Intestine	0.48	0.777	0.629	....	1.508
Gall	Trace	....	.....	....	Trace
Blood	0.914	0 813	0.864	....	....
Muscle	2.68	2.49	2.59	....	3.71
Bones	0.283	0.260	0.272	....	0.871
Pelt	0.568	0.392	0.480	....	0.585
Bone marrow	4.53[1]	0.89[1]	2.71[1]	....	41.7[1]
Testes	....	3.39	....	....	11.27
Adrenals	....	5.54	....	5.36	92.00
Whole animal	0.382[2]	0.4478[2]	....	....	0.8214[2]

Other rabbits	Lecithin, percent of live weight
I	0.3626
II	0.4025
III	0.7995

[1] These determinations were made on fresh substance.
[2] Percent of live weight.

THE PHOSPHORUS OF FETUSES AND NEW-BORN YOUNG

Analyses of the entire bodies of animals dying at birth, or very soon after, have been discussed chiefly in connection with Bunge's suggestion that the composition of the ash of new-born animals generally corresponds with that of the ash of milk, perhaps peculiarly with that of the milk of the same species (Bunge, 1874). Our table shows the ash analyses of Bunge (1874, 1886, 1889) and of Abderhalden (1899c) on the young of several animals, and those of other investigators on new-born human infants. (Giacosa, 1895; deLange, 1897, 1900; Michel, 1899, 1900; Hugounenq, 1899b, 1900; Söldner, 1902.) In this direction the work of Söldner, in conjunction with W. Camerer, Jun., is more extensive than that of others, and their latest results expressed as total grams in the body may be of interest, as given at the foot of the table. (Our figures here are taken from Camerer and Söldner, 1903.)

MINERAL DETERMINATIONS OF THE ENTIRE BODIES OF NEW-BORN INFANTS AND ANIMALS AS REPORTED BY VARIOUS AUTHORS

Species	Author	Date and Reference	Grams per kilogram of body weight											
			K_2O	Na_2O	CaO	MgO	Al_2O_3	Fe_2O_3	Mn_3O_4	P_2O_5	SO_3	Cl	SiO_2	CO_2
Human	Giacosa	1895	0.88	3.35	13.75	0.36	.. .	0.61	....	12.25	....	1.89	....	....
Human	C. deLange	1897	1.94	2.60	11.51	0.41	....	0.50	....	11.13	...	1.88	....	....
Human	Michel	1899, 1900	....	....	13.93	0.405	....	....	....	12.82	....	1.93	....	. ..
Human	Hugounenq	1900	2.29	3.00	14.39	0.55	....	0.15	....	12.54	0.55	1.51	....	....
Human	Söldner and Camerer	1902	1.87	2.04	10.12	0.38	0.03	0.22	0.007	10.01	0.54	1.76	0.02	0.14
Rabbit	Bunge	1874	2.97	1.63	9.59	0.60	....	0.063	....	11.48	....	1.35	....	....
Cat	Bunge	1874	2.79	2.29	9.41	0.42	....	0.067	....	11.10	...	1.97	....	....
Dog	Bunge	1874	2.68	2.59	11.30	0.51	....	0.107	....	12.55	...	2.31	....	....
Dog	Bunge	1889	2.56	2.38	6.60	0.41	....	0.160	....	8.82	....	1.87	....	....
Guineapig	Abderhalden	1899c	2.86	2.40	11.41	1.22	....	0.084 [2]	....	14.76	....	3.34	....	....
Same Computed to Percent of Ash														
Human	Giacosa	1895	2.70	10.23	41.92	1.10	....	1.89	....	37.65	....	5.77	....	....
Human	C. deLange	1897, 1900	6.54	8.80	38.89	1.37	....	1.69	....	37.61	....	6.36	....	....
Human	Michel	1899, 1900	....	....	41.30	1.20	....	[1]	....	38.01	....	5.72	....	....
Human	Hugounenq	1900	6.20	8.12	40.48	1.51	....	0.39	....	35.28	1.50	4.26	....	1.89
Human	Söldner and Camerer	1902	7.06	7.67	38.08	1.43	0.11	0.83	0.03	37.66	2.02	6.61	0.06	0.03
Rabbit	Bunge	1874	10.84	5.96	35.02	2.19	.. .	0.23	....	41.94	....	4.94	....	....
Cat	Bunge	1874	10.11	8.28	34.11	1.52	....	0.24	....	40.23	....	7.12	....	....
Dog	Bunge	1874	8.49	8.21	35.84	1.61	....	0.34	....	39.84	....	7.34	....	....
Dog	Bunge	1889	11.42	10.64	29.52	1.82	....	0.72	....	39.42	....	8.35	....	....
Guineapig	Abderhalden	1899c	8.09	6.79	32.32	3.44	....	0.24 [2]	....	41.79	....	9.46	....	....
Average Content in Grams of Body Weighing 2821 gm. [3]														
Human	Camerer and Söldner	1903	5.29	5.75	28.6	1.07	0.079	0.625	0.019	28.2	1.51	4.96	0.048	0.394

(1) Computed by the compilers.
(2) Mean of 4 computed by the compilers.
(3) Mixed substance of six bodies analyzed and computed to average weight of the bodies.

Michel (1899, 1900) gives two reports of the same analyses of human embryos and fetuses of different stages, and of a new-born infant. We quote the table which gives these analyses on the basis of 100 gm. of fresh substance. These data reflect the rapid deposit of phosphorus which occurs late in fetal life.

COMPOSITION OF HUMAN FETUSES AND A NEW-BORN INFANT
Michel (1899)

Age of fetus Months	Body weight Grams	Percents of fresh substance								
		Water	Nitrogen	Protein (calculated)	Ash	CaO	MgO	P_2O_5	Cl	Fat
2.5	17.80	93.82	0.685	4.39	.....	.....	.....	.....	.....	.....
3.4	125.80	89.95	1.100	7.05	1.729	0.465	0.027	0.489	.....	0.397
5	445	87.80	1.322	8.46	1.948	0.597	0.0258	0.643	0.240	0.888
5	448	86.95	1.390	8.90	2.485	0.790	0.0314	0.842	.....	0.798
6	672	85.02	1.644	10.50	2.512	0.850	0.0328	0.833	.....	1.210
7	1024	84.73	1.563	10.04	2.487	0.804	0.0307	0.788	0.289	1.823
Full term	3335	69.16	2.179	13.96	3.373	1.393	0.0405	1.282	0.193	11.750

Brubacher (1890), in his study of rachitis, gives the following mineral determinations on the entire bodies of two undernourished human fetuses.

BRUBACHER'S ANALYSES OF HUMAN FETUSES
Percents of Fresh Substance

Age of fetus Weeks	Water	Fat	Ash	CaO	MgO	P_2O_5	SiO_2	Fe_2O_3
28	80.75	3.95	3.00	1.04	0.04	1.09	0.01	0.01
36	75.28	8.42	3.12	1.13	0.04	1.15	0.01	0.01

Siwertzow (1909) presents the following data on the lecithin content of the organs of human fetuses and children. He concludes that of the brain, liver, heart and muscles, the brain contains more lecithin than all these other organs put together, the liver coming next, and then the heart, the muscles having least of all. The lecithin content of each of the organs gradually increases in the fetus to a maximum at the time of birth. During the first months of extrauterine life the lecithin remains constant or even decreases, and then rises again, reaching a new, permanent maximum at the second year. The facts established seem to the author to show that in the new-born child there is a store of lecithin, as has been shown for iron, and that this is gradually used up during the first four months.

LECITHIN CONTENT OF ORGANS OF THE HUMAN FETUS AND OF YOUNG CHILDREN (Siwertzow, 1903) Percent, Dry Substance

	Age	Number examined	Brain	Liver	Heart	Muscle
Fetus	6 months	2	9.39	0.25	0.00	1.30
	8 "	1	11.95	2.82	2.22	1.32
	9 "	2	12.86	3.80	3.55	1.38
	10 "	4	16.21	4.90	4.51	2.18
Child	1 month	4	15.66	3.05	2.40	1.54
	2 months	2	15.35	3.20	2.39	1.44
	3 "	2	14.85	2 74	2.44	1.65
	4 "	2	16.40	3.37	2.13	1.58
	6 "	1	17.67	4.83	2.59	1.83
	10 "	1	21.59	5.77	3.93	2.40
	2 years	1	22.78	8.15	7.52	3.86
	3 yrs. 5 mos.	1	23.15	7.58	7.23	4.34

THE PHOSPHORUS OF INFANTS' BODIES AFTER DISEASE

Steinitz (1904) made analyses of the bodies of infants that had suffered serious nutritional disturbances and found them not to differ much, save in fat, from the new-born infants reported by Camerer and Söldner. We give the ash analyses, together with those of Steinitz and Weigert (1904, 1905) on a one-year-old child that had died of tuberculosis with rickets.

ASH ANALYSIS OF BODIES OF INFANTS—Percent of Ash

Case	K_2O	Na_2O	CaO	MgO	Fe_2O_3	P_2O_5	Cl	Cause of death
I	8.3	8.7	37.8	1.1	1.0	39.8	6.5	Nutritional disturbance
II	7.2	7.7	38.1	1.2	1.2	38.7	6.1	" "
III	6.85	7.8	37.8	1.32	0.94	36.3	5.7	" "
IV	6.88	9.03	35.85	0.99	0.425	34.7	7.38	Tuberculosis

Cases I, II and III, Steinitz (1904)
Case IV, Steinitz and Weigert (1904)

THE PHOSPHORUS OF BONES, TEETH, MARROW AND CARTILAGE

REFERENCES TO OLD WORK

Probably the most extensive of the early work on this subject was that of von Bibra (1844) who published a book of 430 pages on chemical studies made by himself and several others on the bones and teeth of men and other vertebrates. Other more or less complete analyses are those of Frerichs (1842), Nasse (1842), Stark (1845), Frémy (1855), von Recklinghausen (1858), Edwards (1860), Zalesky (1866), Papillon (1870, 1870-71, 1873), Volkmann (1873), Mallet (1874), Hofmeister (1873), and Siedamgrotsky and Hofmeister (1879). From Frémy's work we quote the table on the following page.

Schrodt (1876) presents analyses of the individual bones of a normal, healthy dog. The inorganic matter of the water-free bones varied mostly between 60 and 70 percent, but this figure for the sternum was as low as 49.57 percent, and in the third neck vertebra as high as 72.98 percent. In the ash the CO_2 varied between

4.61 and 9.06 percent, the CaO between 50.40 and 53.28 percent, the MgO between 0.78 and 1.08 percent and the P_2O_5 between 39.08 and 40.47 percent. The ratio of calcium carbonate to calcium phosphate is said to be, in compact bones, 1:6.4, and in spongy bones 1:5.7. It is noted that the ash constituents, with the exception of carbonic acid, occur in almost the same quantities in relation to one another in all the bones.

ANALYSES OF BONE OF VARIOUS ANIMALS (Frémy, 1855)—Percent

Animal	Bone	Ash	Calcium phosphate	Magnesium phosphate	Calcium carbonate
Woman	Skull	64.1	57.8	1.7	10.9
Man	Femur	64.2	56.9	1.3	10.2
Egyptian mummy	"	65.0	58.7	1.7	5.9
Dog	"	62.1	59.0	1.2	6.1
Lion, young	"	64.7	60.0	1.5	6.3
Sea-lion		63.1	53.9	1.5	9.3
Rabbit	"	66.3	58.7	1.1	6.3
Elephant, India		66 8	62.2	1.2	5.6
Rhinoceros, Java		65.3	60.0	2 3	5.2
Calf, 5 mos.	Femur	69.1	61.2	1 2	8.4
Cow, old	"	71.3	62.5	2.7	7.9
Ox	Humerus	70.4	61.4	1.7	8.6
Bull	Femur	69.3	59.8	1.5	8.4
Lamb	"	67.7	60.7	1.5	8.1
Sheep	"	70.0	62.9	1.3	7.7
Goat	"	68.0	58.3	1 2	8.4
Sperm whale		62.9	51.9	0 5	10.6
Eagle		70.5	60.6	1.7	8.4
Owl		71.3	61.6	1.5	8.8
Fowl		68.2	64.4	1.1	5.6
Turkey		67.7	63.8	1.2	5.6
Heron		70.6	62.5	1.5	10.2
Teal		73.5	68.4	1.3	5.6
Sea turtle	Carapace	64.0	56.0	1.2	10.7
Crocodile	Bony skin	64.6	58.3	trace	9.7
Carp		61.4	58.1	1.1	4.7
Eel		57.0	56.1	trace	2.2
Ray	Cartilage	30.0	27.7	"	4.3
"	Spines	65.3	64.4	"	1.3
Cod		61.3	55.1	1.3	7.0

COMPOSITION OF THE BONES OF A GANDER (Hiller, 1885)

	Bone	Inorganic matter of fat- and water-free bones Percent	Percent of ash			
			Carbonic acid	Lime	Magnesia	Phosphoric acid
1	Bones of head	58.48	4.67	51.83	0.68	38.90
2	Neck vertebrae	56.64	5.30	51.61	0.77	38.83
3	Back vertebrae	54.99	4.31	52.16	0.83	39.08
4	Caudal vertebrae	47.94	4.03	51.52	0.92	38.86
5	Wish-bone	62.67	5.20	51.57	0.85	39.54
6	Beak bones	60.61	5.36	52.04	0.67	38.63
7	Pelvis	56.72	4.00	52.42	0.75	38.11
8	Ribs	57.11	5.67	51.86	0.80	38.19
9	Scapula	59.45	4.34	52.88	0.67	39 45
10	Sternum	58.91	4.48	52.18	0.81	38.48
11	Right and left humerus	67.16	4.93	52.50	0.81	38.75
12	Right and left radius and ulna	65.91	5.49	52.11	0.84	38.57
13	Right and left metacarpals	61.75	4.48	52.39	0.84	39.28
14	Right and left femur	61.13	4.92	51.30	0.76	38.97
15	Right and left tibia and fibula	62.50	5.47	51.79	0.86	38.50
16	Right and left metatarsals	61.54	5.25	51.66	0.85	38.99
17	Right and left phalanges	55.71	5.35	51.34	0.75	39.53

Hiller (1885) made a similar study (though with less separation of the individual bones) of the bones of a two-and-a-half-year-old gander in normal, average condition. The conclusions were the

same as those of Schrodt, except that the bone showing the highest content of inorganic matter was the humerus, and the ratio of calcium carbonate to calcium phosphate varied, independently of the compactness or sponginess of the substance, between 1:6 and 1:8.

ANALYSIS OF MINERAL MATTER AS OBTAINED BY REMOVAL OF ORGANIC MATTER WITH GLYCERIN AND POTASSIUM HYDRATE

Gabriel (1894) preferred obtaining the mineral matter of bones and teeth by removing the organic matter by heating the powdered bone with alkaline glycerin at 200°C. The substance obtained in this way retains water and carbonic acid which are driven off at the high temperature of ashing. Gabriel says that the mineral matter of bones contains water in two forms, water of crystallization, and water of constitution, the latter not being driven off by heat alone but only by heating with silicic acid.

COMPARISON OF THE MINERAL MATTER OF THE TEETH OF CATTLE AS PREPARED BY ASHING AND BY THE GLYCERIN METHOD
Gabriel (1894)—Percent of Ash

	Treatment	CaO	MgO	K_2O	Na_2O	H_2O of crystallization	P_2O_5	CO_2	Cl
1	Organic matter removed by alkaline glycerin.....	50.68	1.52	0.23	0.97	2.27	38.78	4.16	0.05
2	Organic matter removed by alkaline glycerin.....	50.76	1.52	0.20	1.16	2.21	38.88	4.09	0.05
3	Ashed in the usual way.....	53.67	1.56	0.25	1.13	....	41.55	0.59	0.10
4	(3) computed to H_2O and CO_2 content of (2).....	50.59	1.47	0.24	1.07	2.21	39.13	4.09	0.09

ANALYSES OF "GLYCERIN-ASHES" OF BONES OF DIFFERENT SPECIES (Gabriel, 1894)—Percent of Ash

Animal	Bone	CaO	MgO	K_2O	Na_2O	H_2O of crystallization	P_2O_5	CO_2	Cl
Cattle	Teeth	50.76	1.52	0.20	1.16	2.21	38.88	4.09	0.05
Cattle	Tooth, enamel	51.98	0.53	0.20	1.10	1.80	39.70	3.23	0.21
Cattle	Tooth, dentine	50.36	1.83	0.14	0.80	2.90	38.60	3.97	0.03
Man	Humerus	51.31	0.77	0.32	1.04	2.46	36.65	5.86	0.01
Cattle	Femur	51.28	1.05	0.18	1.09	2.33	37.46	5.06	0.04
Goose	All bones	51.01	1.27	0.19	1.11	3.05	38.19	4.11	0.06

INFLUENCE OF AGE ON THE COMPOSITION OF BONES

The changes in the appearance of bones as an effect of age are so characteristic that anyone who is acquainted with beef recognizes at once the soft vascular bones of young cattle and the white, flinty bones of old animals. Cattle from regions where they are not marketed at an early age are sometimes distinguished from cattle raised in more intensive farming regions by referring to the former as "hard-boned" cattle.

Such data as we have on the changes in composition are all old, but probably they give a fair interpretation of the facts. They are from Weiske and from Wildt (Weiske, 1872a, 1889; Wildt, 1872). With both the birds and the rabbits which Weiske examined the water content of the bones decreased as the animals increased in age, and in the dry bones the mineral content increased and the organic content decreased. The fat content of the water-free bones increased in the rabbit, while in the birds it is said to be larger in the young than in the old fowl. With regard to the composition of the ash, we have computed averages from Weiske's rabbit study.

LIME, MAGNESIA, AND PHOSPHORIC ACID CONTENT OF THE ASH OF RABBIT BONES AT DIFFERENT AGES (Weiske, 1872) Percent

Age	CaO	MgO	P_2O_5
4 weeks	51.24	1 60	42.39
2½ mos.	53.45	1.22	42.23
5 mos.	53.68	1.23	42.47
Adult	54.06	1.07	41.53

Calcium increased, magnesium decreased and phosphorus remained nearly constant in the ash. The same relations held in Weiske's data on bird bones.

Weiske (1889) analyzed the bones of fowls of various ages, all receiving grain food. These results show with increasing age an increase of all the mineral constituents in the dry, fat-free bone. In the ash, there were increased percentages of CaO and CO_2 and decrease in MgO.

COMPOSITION OF THE BONES OF FOWLS AS AFFECTED BY AGE Weiske (1889) Percent, Dry, Fat-free Bone

Age	Mineral matter	P_2O_5	CaO	MgO
Just hatched	25.29	9.31	10.57	0.36
1 week	32.77	13.45	15.35	0.47
2 weeks	37.40	14.84	17.68	0.54
4 weeks	42.59	17.19	20.42	0.63
8 weeks	44.92	17.79	21.97	0.62
12 weeks	42.27	16.43	20.68	0.49
18 weeks	46.57	17.48	23.32	0.49
24 weeks	40.12	14.70	19.99	0.33
34 weeks	48.71	18.25	24.47	0.40
44 weeks	57.14	22.25	28.98	0.61
52 weeks	54.20	19.98	27.86	0.43
52 weeks	57.05	21.73	28.99	0.58

Wildt (1872) reported analyses of the ash of the bones of rabbits of various ages. The following table is from this work. The inorganic substance increased with age as also did the calcium and the carbonic acid, while magnesium and phosphorus diminished.

ANALYSES OF THE ASH OF THE BONES OF RABBITS OF DIFFERENT AGES (Wildt, 1872)

Age of rabbits	Inorganic substance [1] Percent	Percent of ash				Inorganic substance in fresh bone Percent
		Carbonic acid	CaO	MgO	Phosphoric acid	
New-born	53.39	3.65	52.17	1.38	42.05	15.56
3 days	50.82	3.84	52.16	1.36	42.13	17.23
14 days	55.18	3.99	52.10	1.26	42.19	18.62
1 month	58.94	4.00	51.91	1.22	42.20	23.39
2 months	65.63	4.52	52.10	1.09	41.64	30.13
3 months	67.68	4.69	52.49	1.01	41.03	30.90
4 months	68.72	4 92	52.60	1.02	40.80	37.17
6 months	70.26	4.94	52.64	1.05	40.80	41.80
8 months	71.77	5.54	52.78	0.93	40.05	39.22
1 year	74.24	5.71	52.61	0 91	40.04	44.39
2 years	72.90	5.81	52.76	0.93	39.78	41.68
3-4 years	73.65	5.66	52.84	0.83	39.80	45.00

(1) Apparently reckoned on residue from water-extraction of fat-free bone.

See also Graffenberger (1891).

COMPOSITION OF THE TEETH

Hoppe-Seyler (1862) submits a table of analyses (p. 117) of the enamel of the teeth of several species of animals. General similarity is evident.

Kühns (1895) compares human teeth at different ages. The more notable differences are in the calcium and magnesium of the enamel, the former increasing and the latter decreasing with age, and the increase with age of the phosphorus of the dentine. (P. 116.)

Bertz (1899) says that in teeth the bases were found to exceed the acids; that, contrary to the findings of others, no alkalis or carbonates were found; that there is no chlorine in enamel; that it is doubtful if there is a trace of chlorine in true dentine; and that dentine is found to contain twice as much magnesia and half as much fluorine as enamel. (See table on next page.)

St. Bondzyński and Gońka (1907) found that the organic substance of calf teeth, entirely freed from mineral matter, contained 0.37 percent phosphorus. The ground-substance of bone (femur of horse) similarly treated showed no organically combined phosphorus.

For other analyses of teeth see Gabriel, p. 113, Gassmann (1908) and C. Cohn (1889), under Caries, and also Weiske (1891b, 1892, 1894, 1895c, 1896, 1897), Graffenberger (1891), Carnot (1892) and Aeby (1873c).

COMPARISON OF HUMAN TEETH AT DIFFERENT PERIODS OF LIFE
Kühns (1895)

Age	Enamel						Dentine					
	Water	Loss on ignition	Percent of ash				Water	Loss on ignition	Percent of ash			
	Percent	Percent	CaO	MgO	P_2O_5	Fl	Percent	Percent	CaO	MgO	P_2O_5	Fl
6-yr. molar	2.45	8.39	52.58	1.08	36.89	0.29	10.46	24 09	53.38	2.41	37.38	0.25
Normal adult	1.12	7.36	53.75	0.84	37.2	0.29	9 04	23.06	53.42	2.41	39.46	0.25
Senile	1.34	6.85	55.37	0.66	36.26	0.29	9.23	22.21	53.46	1.81	39.97	0.25

ANALYSES OF HUMAN AND CALF TEETH (Bertz, 1899)

Kind of teeth	Enamel							Dentine						
	Total dry substance	Percent of dry substance						Total dry substance	Percent of dry substance					
	Percent	Organic	CaO	MgO	P_2O_5	SO_3	Fl	Percent	Organic	CaO	MgO	P_2O_5	SO_3	Fl
Human	98.193	6.822	50.224	0.732	40.693	0.296	1.089	90.811	29.15	38.180	1.508	30.244	0.378	0.471
Calf	93.976	16.56	44.243	0.955	37.019	0.316	0.771	....	....	....	....	....	....	....

COMPOSITION OF THE ENAMEL OF TEETH
Hoppe-Seyler (1862) Percent of Inorganic Matter

Animal	Age	P_2O_5	CaO	MgO	Cl	Fe_2O_3
Man	New-born	30.53	41.42	0.72	Trace	?
Man	New-born	35.69	44.91	0.79	0.15	0.34
Man	New-born	36.61	45.03	0.50	?	Trace
Hog	Young	39.06	48.67	0.74	0.30	0.48
Hog	Adult	40.59	51.57	0.91	0.40	0.47
Rhinoceros	Fossil	40.57	51.23	0.75	0.42	1.30
Elephant	Fossil	38.85	49.71	0.92	0.28	0.29
Mastodon	Fossil	39.62	52.82	0.30	0.38	0.17
Paleotherium	Fossil	40.20	52.39	0.59	0.37	0.40
Horse	....	40.22	51.10	0.56	0.43	Trace
Dog	....	43.63	51.46	2.27	0.51	?

PHOSPHORUS COMPOUNDS OF BONE

The Inorganic Phosphate. From all of these analyses it is quite evident that lime and phosphoric acid are the principal constituents of the mineral part of bones, the two together forming fully 90 percent of the ash. Carbonic acid and magnesia are also certainly present, and there is no doubt that these are united as some form of calcium phosphate, magnesium phosphate and calcium carbonate. There are also small quantities of sodium, potassium, chlorine and fluorine.

Papillon (1870, 1870-71, 1873) claims to have introduced strontium, magnesium and aluminum, and H. Stoelzner (1908) strontium, into bones in place of a small part of the calcium.

Attempts have been made to assign definite formulae to the calcium phosphate and to a combination of phosphate and carbonate of calcium; but, so far as we know, none of these have been on any other basis than the percentage composition. Other chemical and physico-chemical evidence should be brought out before confidence is placed in any formula claiming to represent chemical union of the elements in the usual sense.

The articles in which we have noted that attention was given to this subject are: Berzelius, 1816; von Gohren, 1865; Aeby, 1872a, 1872b, 1873a, 1874a, 1874b; Wibel, 1874; Schrodt, 1876; Levy, Moritz, 1894; Gabriel, 1894; Gassmann, 1910, 1913.

Gabriel's conclusion, after his studies on the mineral constituents of bones and teeth, the organic matter being removed by the glycerin method, which avoids high temperatures, he expresses in this way: "The composition and properties of bone and tooth-ash

have their simplest expression in the formula ($Ca_3(PO_4)_2 + Ca_5HP_3O_{13} + Aq$), in which 2—3 percent of the lime is replaced by magnesia, potash and soda, and 4—6 percent of the phosphoric acid by carbonic acid, chlorine and fluorine."

Gassmann favors the formula $\left[Ca\left(\begin{matrix}OPO_3Ca\\ \diagdown\ Ca\\ \diagup\ OPO_3Ca\end{matrix}\right)_3\right]CO_3$,

(which he attributes to A. Werner) on account of having found the ratio of the three constituents constant in this proportion in normal and in rachitic bones, and from having isolated from an ignited mixture of ground teeth and calcium chloride a compound corresponding in its chemical analysis to the analogous chloride. To account for the increased proportion of Mg in rachitic bones Gassmann suggests that this does not belong to a salt-forming body.

Lecithin and Phosphorus Determinations on Bone Marrow. A part of the fat of bone marrow is phosphorized, and on the older understanding, which called all the phosphatids lecithin, and computed the amount of lecithin from the percent of phosphorus found in the alcohol-ether extract, lecithin determinations on bone marrow are reported. Otolsky (1906) and Bernazky (1908) have studied in particular the composition of the lecithin of bone marrow. From these articles we have seen only abstracts. One kilogram of bone marrow yielded by Otolsky's process 1.3-1.5 gm. lecithin, containing 3.25 percent phosphorus, and yielding choline, glycerophosphoric acid and fatty acids on cleavage.

Bernazky considered the distribution of phosphorus in the organs of the horse, and made a special study of the lecithin of bone marrow. He says that the red bone marrow of the horse contains twice as much lecithin as the white bone marrow, and that no differences were observed in either the amount or the composition of lecithin in the bone marrow of horses immunized against diphtheria, scarlet fever and the yellow staphylococcus.

Hutchison and MacLeod (1901-2) studied the red marrow from the ribs of the horse. They report that the fat, lecithin and cholesterin together constituted 17.9 percent of the marrow, the soluble salts 2.34 percent and the insoluble salts 0.66 percent. Among the soluble salts was included 0.48 percent P_2O_5. A nucleoproteid was found.

Nerking (1908a) found, of lecithin, in red bone marrow, 0.1576, 0.1469, and 0.3006 percent, and in yellow bone marrow, 0.1636 and 0.2046 percent.

Glikin (1907, 1908a, 1908b, 1909a) made a number of Fe_2O_3, P_2O_5 and lecithin determinations on the fat of the bone marrow of different kinds of animals at different ages which seem to support the view that the marrow of very young animals is richer in lecithin than that of older animals, and that it is highest in the young of those species which are most helpless at birth.

PHOSPHORUS, IRON AND LECITHIN DETERMINATIONS ON THE FAT OF BONE MARROW OF SEVERAL SPECIES OF ANIMALS AT DIFFERENT AGES (Glikin, 1907) Percent

Animal	Age	P_2O_5	Fe_2O_3	Lecithin	
Cattle	Older	0.1152	0.0243	1.31	
Cattle	Older	0.2309	0.0266	2.62	
Cattle	Older	0.2378	0.0283	2.70	
Cattle	Older	0.2010	0.0223	2.28	
Calf	Younger	0.2515	0.1105	2.86	
Calf	Younger	0.3193	0.1085	3.63	
Calf	Younger	0.3198	0.1254	3.64	
Calf	Younger	0.5950	.....	6.76	
Horse	18 yrs.	0.0787	0.0254	0.89	
Horse	.....	0.0963	.....	1.09	
Horse	10 yrs.	0.1055	0.0379	1.20	
Horse	6-7 yrs.	0.1749	0.0975	1.98	
Horse	7-8 yrs.	0.1709	0 0750	1.94	
Horse	2 yrs.	0.3741	0.0486	4.25	
	Foal	0.1842	.....	2.09	
Swine	Older	0.2092	0.0396	2.38	
Swine	Older	0.2105	0.0264	2.39	
Swine	Older	0.1992	0.0145	2.96	
Swine	Young	0.4564	.....	5.18	
Pigs	20 hrs.	2.6538	1.29	30.16	
Pigs	24 hrs.	2.7413	1.02	31.16	
Pigs[1]	6 wks.	4.1555	0.2960	47.23	[1]Bottle nursed
Pigs[2]	8 wks.	2.5834	.....	29.36	[2]Badly nourished
Pigs	8 wks.	2.4800	0.1460	28.19	
Sheep	Older	0.1529	0.0138	1.73	
Sheep	Older	0.2253	0.0191	2.56	
Sheep	Younger	0.3254	0.0249	3.70	
Sheep	Younger	0.5732	0.0839	6.51	
Dog	Older	0.3235	0.1672	3.67	
Dog	Older	0.1777	0.0542	2.02	
Dog	Older	0.3081	0.0489	3.50	
Dog	5 wks.	1.6418	0.4437	18.66	
Dog	Stillborn	3.3170	4.35 !	37.70	
Dog	10 wks.	0.8376	0.3214	9.52	
Man[3]	88 yrs.	0.1613	0.0354	1.83	[3]Lung emphysema
Man[4]	70 yrs.	0.2433	0.1157	2.76	[4]Stomach, liver, kidney cancer
Man[5]	70 yrs.	0.2052	0.0668	2.38	[5]Pleurisy
Man[6]	61 yrs.	0.1947	0.0693	2.21	[6]Influenza, inflammation
Man[7]	56 yrs.	0.1783	0.0807	2.02	[7]Kidney inflammation, enlargement of the heart
Man	34 yrs.	0.2905	0.0552	3.30	
Child[8]	2 yrs.	1.1770	1.025	13.38	[8]Pleurisy
Child[9]	16 mos.	2.1930	0.2237	24.93	[9]Bronchopneumonia
Child[10]	13.5 mos.	2.5730	.....	29.24	[10]Lung emphysema
Child[11]	7 mos.	5.3839	0.8049	61.19	[11]Pneumonia
Cat	New-born	2.919		33.18	
Rabbit	New-born	2.306		26.21	
Guineapig	New-born	1.520		17.34	
Bird	Young	2.25		25.63	

Bolle (1910a, 1910b) submits many lecithin estimations on the marrow of several species of animals, and says that his findings agree with those of Glikin in that lecithin seems to be always present in the fat of bone marrow, the amount decreasing with advancing age, and that in paralysis there is an impoverishment in this particular. The tables did not seem to the abstractor to show clear

evidence of decrease with age, at least they did not exhibit anything like a regular gradation of lecithin according to age. The method of lecithin estimation is open to considerable improvement.

Suzuki and Yoshimura (1907) found lecithin in bones, and also, an acid-soluble organic phosphorus compound.

For other lecithin figures on bone marrow see Glikin 1909a, under Phosphorus Metabolism in Paralysis.

Phosphorus Compounds in Cartilage. Grandis and Copello (1902) state that the epiphyseal cartilage of the femur and tibia of the calf, compared with the articular cartilage, contains decidedly more phosphorus, a part of which is held in organic combination.

PHOSPHORUS COMPOUNDS OF MUSCLES

The studies on the amounts of phosphorus in muscles, and on the forms in which it is present, have a two-fold significance, (1) as related to the phosphorus requirement of the organism, and (2) as bearing on the value of meats as foods. Muscles contain phosphorus in the forms of nucleoproteins, phosphatids, nucleon (phosphocarnic acid) and inorganic phosphates.

STUDIES OF THE AMOUNT AND DISTRIBUTION OF PHOSPHORUS

Katz's (1896) ash analyses on muscle are often quoted because his was the first extensive study of the kind, and it covers many species of animals. (See table on following page.)

More recent studies are those of Grindley and associates, from the latest of which, by L. D. Hall and Emmett (1912), we quote the following:

PHOSPHORUS IN THE BONELESS FLESH OF DIFFERENT CUTS OF BEEF (Hall and Emmett, 1912) Percent

Wholesale cuts	Soluble phosphorus			Insoluble	Total
	Inorganic	Organic	Total soluble		
Round	0.093	0.032	0.125	0.059	0.184
Clod	0.094	0.033	0.127	0.046	0.173
Hind shank	0.085	0.024	0.109	0.052	0.161
Chuck	0.091	0.015	0.106	0.052	0.158
Neck	0.085	0.013	0.098	0.050	0.148
Fore shank	0.092	0.016	0.108	0.033	0.141
Loin	0.072	0.017	0.089	0.053	0.142
Rump	0.062	0.022	0.084	0.051	0.135
Rib	0.065	0.019	0.087	0.043	0.130
Plate	0.050	0.015	0.065	0.039	0.104
Flank	0.048	0.006	0.054	0.023	0.077

See also Grindley and Emmett (1905), Emmett and Grindley (1906, 1909a, 1909b).

For materials on the phosphorus compounds of the muscle of swine, as affected by foods, see Hart, McCollum and Fuller (1909) under Nutr. Val. Org. and Inorg. P., and Forbes (1909) under Comm. Foods in Rel. to P. Met.

MINERAL ELEMENTS OF FLESH OF VARIOUS ANIMALS

Katz (1896) Percent

Animal	Water Percent	Percent of dry substance										
		Potassium	Sodium	Iron	Calcium	Magnesium	Phosphorus				Chlorine	Sulphur
							Total	In water extract	In alcohol extract	In residue		
Man	72.53	1.1659	0.2906	0.0535	0.0273	0.0771	0.7406	0.5216	0.1394	0.0797	0.2552	0.7576
Pig	72.89	0.9363	0.5752	0.0218	0.0298	0.1042	0.7848	0.5634	0.1360	0.0854	0.1787	0.7536
Ox	75.80	1.5200	0.2695	0.1019	0.0088	0.1006	0.7090	0.5092	0.1171	0.0827	0.2342	0.7719
Calf	75.39	1.5444	0.3492	0.0356	0.0587	0.1237	0.8928	0.5929	0.1716	0.1283	0.2733	0.9178
Deer	75.27	1.3586	0.2848	0.0423	0.0388	0.1175	1.0053	0.7266	0.1700	0.1087	0.1637	0.8517
Rabbit	76.53	1.7179	0.1974	0.0233	0.0790	0.1240	1.0922	0.8838	0.1281	0.0804	0.2206	0.8500
Dog	76.42	1.4178	0.4000	0.0193	0.0291	0.1005	0.9478	0.6423	0.2037	0.1018	0.3415	0.9643
Cat	75.14	1.5576	0.2932	0.0372	0.0341	0.1152	0.8106	0.6192	0.1166	0.0748	0.2257	0.8748
Hen	68.38	1.4700	0.3008	0.0295	0.0333	0.1174	0.8164	0.6449	0.0790	0.0926	0.1904	0.9234
Frog	81.62	1.6756	0.3005	0.0339	0.0852	0.1280	1.0130	0.8288	0.1126	0.0717	0.2190	0.8835
Haddock	80.64	1.7281	0.5118	0.0300	0.1138	0.0863	0.7067	0.5927	0.0655	0.0485	1.2447	1.1514
Eel	63.10	0.6519	0.0812	0.0148	0.1061	0.0483	0.4796	0.3980	0.0549	0.0267	0.0935	0.3657
Pike	79.38	2.0176	0.1426	0.0209	0.1929	0.1505	1.0285	0.8305	0.0755	0.1226	0.1548	1.0576

A. Kossel (1882) reported the following estimations of total and nuclein phosphorus in the muscle of cattle and hens.

TOTAL AND NUCLEIN PHOSPHORUS IN MUSCLE
Kossel (1882) Percent

	Species	H_3PO_4 in fresh organ	Nuclein H_3PO_4	Nuclein H_3PO_4 in total H_3PO_4	
Embryonic muscle	Cattle	0 462	0 1490	32.2	Embryo 28 cm. long
Muscle	Cattle	0.610	0.0923	15.1	
Muscle	Hen, fasted	0.838	0 0542	6.5	
Muscle	" well fed	0.663	0 0442	6.7	

The distribution of phosphorus in the muscle of salmon in normal condition is reported by D. Noël Paton and his associates (Paton, 1898; Paton et al. 1897-98) as follows:

DISTRIBUTION OF PHOSPHORUS IN MUSCLES OF SALMON
Paton, et al. (1897-98) Percent

Fish number	Type of muscle	Ether extract "Lecithin"	Water extract, "Phosphates"	Residue, "Nucleins and pseudonucleins"	Total
14	Thick	0.042	0.131	0.056	0.228
14	Thin[1]	0.046	0.094	0.041	0.181
76	Thick	0.060	0.095	0.055	0.210
76	Thin	0.060	0.119	0.063	0.242

(1) The "thin" muscle is said to comprise about ¼ of the entire body.

Milroy's (1908) determinations on the muscle of herring show wide and irregular variations from month to month, ranging from 0.45 to 0.82 percent P_2O_5 in fresh muscle.

Urano (1907) has made complete mineral analyses of the muscular tissue of frogs, and also of the press juice from the same, the blood plasma, and the muscle extraction residue. The salts of the blood and lymph in the muscle were removed by treatment with isotonic (6 percent) cane sugar solution; after which the muscle juice was expressed by a pressure of 1000 atmospheres. This press juice was dried, and extracted with hot water, and the extract and residue analyzed separately. Blood plasma was prepared by centrifuging. The phosphorus figures are as stated below:

PHOSPHORUS IN MUSCLE OF FROG—Percent PO_4

Sample		Juice	Ash	Muscle
A	Sugar muscle	0.378	69.399	0.2268
B	Fresh muscle	0.633	64.9	0.3861
	Sugar muscle	0.368	76.9	0.2245
C	Fresh muscle	0.422	48.0	0.2532
	Sugar muscle	0.311	63.8	0.2084
D	Fresh muscle	0.529	60.849	0.529
	Fresh muscle	0.531	60.236	0.531
	Blood plasma	0.109	16.732	0.109
	Expressed juice, ashed	0.432	52.558	0.432
	Expressed juice, dialyzed	0.468	55.469	0.468

Richet (1900) analyzed beef muscle serum. A kilogram of the serum contained 8.9 gm. ash, of which 3.15 gm. was P_2O_5. The form in which the phosphorus was present in the serum was not determined.

Whitfield (1894) made a special examination to determine whether the myosin of muscle is a nucleoalbumin and whether there is any nucleoalbumin in muscle, and decided that myosin is not a nucleoalbumin and that muscle contains no nucleoalbumin. Pekelharing (1896), however, isolated from the muscles of rabbit, dog and ox substances which he identified as nucleoprotein.

Martin Müller's (1897) nucleon determinations in human muscle vary from 0.1123 to 0.2174 percent, in the muscle of adults, and from 0.0000 to 0.0570 in the muscle of new-born infants. Panella (1902a, 1903b, 1903e, 1903f, 1904b, 1906b) decided that phosphocarnic acid is a constant, normal constituent of the striated muscles of dogs and rabbits, being found in both the red and the white muscles of rabbits; but his paper of 1906 throws doubt on the quantitative value of all earlier determinations, as they may have been made on too small samples. The amounts reported at that time are 0.01 percent of fresh and 0.02-0.03 percent of dry muscle.

Bajmakov (1904) (through Biochem. Centralbl.) reports analyses of the muscles of calves (5) and of children (9) of different ages, which show that the dry substance, ash, phosphorus and iron content of muscle, as well as the total protein and "organized protein," increase with advancing age. The iron is said to increase at a more rapid rate than the phosphorus.

MacLean (1912b) has made a careful purification and examination of the phosphatids of horse muscle, and decides that the chief one present is a lecithin, the proportion of N:P being as 1:1.

Cavazzani (1904b) found the phosphocarnic acid content of oysters to vary with the stages in the life cycle from 0.1942 to 0.5978 percent with a mean value of 0.3725.

COMPARISONS OF STRIATED AND NON-STRIATED MUSCLES

There seem to be differences in chemical composition between the striated, or voluntary, and the non-striated, or involuntary muscles; and the heart muscle (myocardium), which is striated but involuntary, differs somewhat from both. The reports as to these differences are not closely concordant, but we give such as there are.

Saiki (1908) was apparently the first to make determinations on the mineral constituents of non-striated mammalian muscle. He used the same analytical methods as Katz. Saiki is alone in finding the sodium content higher than the potassium in non-striated muscles, so far as we know, though others do find somewhat more of sodium and more of chlorine than in striated muscles.

MINERAL ANALYSES OF NON-STRIATED MUSCLES OF PIG
Saiki (1908)

Source	Water	Percent, dry, fat-free substance							
	Percent	K	Na	Fe	Ca	Mg	Cl	S	P
Stomach I	81.4	0.415	1.549	0.028	0.111	0.026	0.922	0.444	0.381
Stomach II	80.8	0.332	1.095	0.036	0.117	0.023	0.808	0.445	0.428
Urinary bladder I	80.6	0.342	1.058	0.042	0.205	0.013	0.816	0.424	0.416
Urinary bladder II	79.6	0 204	1.045	0.049	0.187	0.012	0.786	0.373	0.437
Average	80.6	0.323	1.187	0.039	0.155	0.019	0.833	0.422	0.416

Edw. B. Meigs and L. A. Ryan (Meigs and Ryan, 1912; Ryan and Meigs, 1912) report finding in the water-extract of the smooth muscle of the stomach of the frog (*Rana catesbiana*) 0.0958 and 0.0919 parts phosphorus per 100 parts of muscle; in the alcohol extract 0.0356 and 0.0260 parts, and in the residue 0.0146 and 0.0105 parts, making in the whole muscle 0.1460 and 0.1284 parts phosphorus. They conclude that "1. The fibres of this tissue are not surrounded by semi-permeable membrane. 2. Most of the water of the smooth muscle fibres is held by the colloids of the living tissue as organic water. 3. Most of the potassium, phosphorus, sulphur, and magnesium, which appear in the ash of smooth muscle, are present in the living tissue in a non-diffusible form." A large portion of the phosphorus is thought to be in the form of lipoid. The following are their ash analyses of striated and smooth muscles of the frog:

MINERAL CONSTITUENTS OF SMOOTH AND STRIATED FROG MUSCLE
Meigs and Ryan (1912) Percent, Fresh Basis

	K	Na	Fe	Ca	Mg	P	Cl	S	H_2O
Striated I	0.3483	0.0572	0.0099	0.0335	0.0288	0.1554	0.0650	0.1492	79.99
Striated II	0.3518	0.0500	0.0094	0.0228	0.0313	0.1541	0.0674	0.1322	79.74
Average	0.3500	0.0536	0.0096	0.0281	0.0300	0.1547	0.0662	0.1407	79.87
Smooth I	0.3063	0.0648	0.0007	0.0042	0.0132	0.1460	0.1191	0.1724	82.61
Smooth II	0.3437	0.0804	0.0007	0.0042	0.0126	0.1284	0.1200	0.1501	82.01
Average	0.3250	0.0726	0.0007	0.0042	0.0129	0.1372	0.1195	0.1612	82.30

According to Vincent's (1902) comparison of the proteins of smooth and striated muscles, the smooth contain 6-8 times as much nucleoprotein as the striated, and the heart muscle has an intermediate place in this regard. Panella (1904b) found more nucleon in non-striated than in striated muscles. Balke and Ide (1896) found in the heart of the horse 0.116 and 0.105 percent, and in that of the dog 0.253 percent of nucleon.

Krehl (1893) found that the lecithin content of the healthy heart muscle is about constant at 4.2 to 4.6 percent, while in different maladies it varies from 1.1 to 6.3 percent without reference to the state of nutrition.

Rubow (1905) studied the composition of the heart and of ordinary striated muscle as affected by various conditions. From this investigation we quote the following data which show heart muscle to be richer in lecithin than is skeletal striated muscle.

LECITHIN CONTENT OF HEART AND ORDINARY STRIATED MUSCLE
Percent of Muscle

Subject and condition	Muscle	No. of subjects	Ether extract	Lecithin	Fat
Dog, well fed	Heart	9	12.23	8.01	4.21
Dog, starved 19-22 days	Heart	2	11.18	7.49	3.69
Dog, well fed	Striated		10.07	5.08	5.99
Dog, starved 19-22 days	Striated	2	6.07	3.41	2.66
Lamb, normal	Heart	1	18.71	7.54	10.17
Lamb, normal	Back	1	15.03	2.50	12.53
Lamb, normal	Heart	1	17.62	8.02	9 60
Lamb, normal	Shoulder	1	14.54	4.15	10.39

Erlandsen (1906, 1907) made an exhaustive study of the phosphatids of muscle from the heart and from the upper thigh of the ox, distinguishing different kinds of phosphatids. Both forms of muscle contained lecithin, a little of a protagon- or jecorin-like substance, a new monamino-diphosphatid, "cuorin," and a diamino-monophosphatid. Phosphorus was also found as phosphocarnic acid, inorganic salts and in some nitrogenous relation not identified. The heart muscle was the richer in phosphatids in general, and especially in the two new phosphatids. A high content of cuorin seems to be characteristic of heart muscle. It contains less of phosphocarnic acid than the thigh muscle. The phosphatids were thought to be present in both types of muscle partly in a free state and partly combined with protein.

From the values given in the table below, Costantino (1912) draws the conclusions:

"1. There is no measurable variation between striated and non-striated muscle in respect to total phosphorus. Heart muscle tissue shows, however, a higher percentage of phosphorus.

"2. There is an important difference in respect to plain and striated muscle content of inorganic phosphorus. Plain muscle contains about the same amounts of organic and inorganic phosphorus; striated muscle contains a much higher percentage of inorganic than organic phosphorus. Heart muscle shows the same relation as plain muscle.

"3. Both the plain and heart muscle tissue show higher values of organic than phosphatid phosphorus. Phosphatid phosphorus is shown to be about ½ as much as organic phosphorus in plain muscle, and only ⅓ as much in case of muscle fibres of cow's uterus."

PHOSPHORUS OF STRIATED AND NON-STRIATED MUSCLE OF CATTLE (Costantino, 1912)

Type	Muscle	Percents of dried muscle					Percents of total phosphorus			
		Total phosphorus	Inorganic phosphorus	Organically combined phosphorus	Phosphatid phosphorus	Organic, not phosphatid	Inorganic phosphorus	Organic phosphorus	Phosphatid phosphorus	Organic, not phosphatid
Striated.....	?	0.7575	0.6126	0.1449	0.1242	0.0207	81.50	18.50	16.39	2.11
	?	0.6498	0.5287	0.1211	0.1059	0.0152	81.36	18.64	16.29	2.35
	Heart	1.0814	0.4327	0.6487	.....	.....	40.01	59.99	.....	....
	Heart	1.0430	0.3951	0.6479	0.4407	0.2072	37.88	62.12	42.25	19.87
Non-striated	Retractor penis	0.5670	0.2313	0.3357	.....	.....	40.79	59.21	.....	.....
	Retractor penis	0.5917	0.2839	0.3078	0.1439	0.1639	47.97	52.03	24.33	27.70
	Stomach	0.6010	0.3148	0.2862	0.1518	0.1344	52.38	47.62	25.25	21.37[1]
	Stomach	0.5751	.....	.....	.....	.....	.....	.....	.....	.....
	Uterus	0.8449	0.3353	0.5096	0.1644	0.3452	39.68	60.32	19.46	40.86
	Uterus	0.7329	0.2142	0.5187	0.2081	0.3106	29.22	70.78	28.39	42.39

(1) The compilers compute this to be 22.36.

MacLean (1913) found heart muscle to contain lecithin, cuorin and a trace of diamino-monophosphatid which resembles the substance described by Stern and Thierfelder and by Thudichum. An analogous compound has been obtained from kidneys by Dunham and Jacobson and by MacLean.

For the distribution of phosphorus, potassium and chlorine within the muscle fiber see Menten (1909).

PHOSPHORUS IN FEATHERS

In connection with Weiske's study (1889) of the effects of age on the composition of the bodies of birds, analyses were made of the feathers. From the following data it appears that as a growing fowl increases in age the phosphorus of the feathers decreases in percentage during the first 18 weeks. At the 18th week the feathers contain a lower percentage of mineral matter generally than at any other time during the first year, and this is also the low point for percentage content of calcium, sulphur and phosphorus.

ANALYSES OF FEATHERS OF BIRDS
Weiske (1889) Percent of Dry, Fat-free Feathers

Bird	Age, weeks	Mineral matter	CaO	MgO	SO_2	P_2O_5	Feed
Fowl	0	2.04	0.31	0.140	0.11	0.190	Corn
Fowl	1	1.98	0.16	0.051	0.23	0.190	Corn
Fowl	2	2.19	0.45	0.047	0.48	0.160	Corn
Fowl	4	2.09	0.40	0.120	0.27	0.150	Corn
Fowl	8	1.51	0.15	0.044	0.25	0.140	Corn
Fowl	12	1.50	0.19	0.050	0.14	0.140	Corn
Fowl	18	0.88	0.15	0.022	0.052	0.060	Corn
Fowl	24	1.80	0.40	0.049	0.059	0.117	Corn
Fowl	34	1.78	0.62	0.024	0.10	0.075	Corn
Fowl	44	2.11	0.87	0.011	0.22	0.067	Corn
Fowl	52	1.82	0.82	0.031	0.15	0.062	Corn
Fowl	52	1.89	0.80	0.041	0.13	0.070	Corn
Falcon		0.40	0.050	0.016	0.037	0 074	Meat
Buzzard		0.62	0.092	0.006	0.147	0.133	Meat

THE PHOSPHORUS OF BRAIN, NERVES AND CEREBROSPINAL FLUID

HISTORICAL REVIEW TO THE TIME OF THUDICHUM

None of the general analyses of brain before those of Thudichum need receive especial attention. Thudichum mentions one by Hensing (1719) when the phosphorus of the brain was discovered. Fourcroy's (1793) work was quite extensive and Vauquelin's (1811) was significant enough to have led to its translation from the French into both English and German, and to be reviewed at some length in Thudichum's "Die chemische Konstitution des Gehirns." Couerbe's (1834) analyses were followed by Frémy (1841, 1842). We find early ash analyses by Breed (1851b) and by Geoghegan (1877-78). VonBibra (1853, 1854a) made phosphorus determinations on the fat obtained from the brains of fifteen kinds of animals, and of men, and showed that this phosphorus is a constituent of the fat itself. The next year (vonBibra, 1854b) he reports phosphorus in the spinal cord and nerves of several species, and concludes that in brain and spinal marrow the phosphorus content depends on the fats containing phosphorus, and in nerves principally on the cerebric acid. Liebreich's (1865) analysis is significant for its discovery of protagon, which, however, is now known not to be a single compound. After Gobley and others made the various studies of "lecithin," Gobley (1877) reported a general analysis of brain. The later one of Gutnikov (1896-97) should also be mentioned.

Some of these old reports make interesting reading. Couerbe (1834), finding a lower phosphorus content in the fat of an idiot's brain and a higher in that of the insane than normal, concludes: "Phosphorus is the exciting principle of the nervous system," and

Note: For general discussions of the subject of the chemical composition of the brain and nerves the reader is referred to Thudichum (1901), Halliburton (1901b, 1905) Coriat (1905) and Fränkel (1909a).

"Absence of phosphorus from the brain reduces man to the level of the brute, while a great excess irritates the nervous system, causing mental alienation."

THE WORK OF THUDICHUM

At the time of his report in 1875 Thudichum (1875) had analyzed a thousand brains, mostly normal brains from human subjects, and had found and identified many of the compounds which he afterwards described and classified more fully. "Die chemische Konstitution des Gehirns" appeared in 1901 and seems to have greatly stimulated and influenced later work on brain chemistry in general and especially on the chemistry of lipoids. The classification of compounds found is given below; also analytical determinations of the principal constituents of the white and the gray matter:

THUDICHUM'S CLASSIFICATION OF THE BRAIN CONSTITUENTS

A. GROUP OF PHOSPHORUS-CONTAINING CONSTITUENTS OR PHOSPHATIDS

- Subgroup of the monophosphatids containing one nitrogen. N:P=1:1.
  - Lecithin
  - Cephalin
  - Paramyelin
  - Myelin
- Subgroup of monophosphatids containing two nitrogens. N:P=2:1
  - Amidomyelin
  - Amidocephalin
  - Sphingomyelin
  - Apomyelin
- Subgroup of diphosphatids containing two nitrogens. N:P=2:2.
  - Assurin
- Subgroup of nitrogen-containing phosphatid-sulphatids
- Subgroup of nitrogen-free monophosphatids
  - Lipophosphoric acid
  - Butophosphoric acid

B. GROUP OF NITROGEN-CONTAINING PHOSPHORUS-FREE CONSTITUENTS

- Subgroup of cerebrosids or cerebrogalactosids
  - Phrenosin
  - Kerasin
- Subgroup of cerebrin acids
  - Cerebrinic acid
  - Sphaerocerebrin
- Subgroup of cerebrosulphatids
- Subgroup of amidolipotids or nitrogen-containing fats
  - Bregenin
  - Krinosin
- Subgroup of alkaloids
  - Hypoxanthin
  - Gladiolin
  - Tenysin
- Subgroup of amino acids and amids
  - Leucin and its homologues
  - Tyrosin
  - Urea

C. GROUP OF CONSTITUENTS WHICH CONTAIN ONLY THREE ELEMENTS

- Subgroup of nitrogen-free alcohols
  - Cholesterin
  - Phrenosterin (?)
- Subgroup of carbohydrates
  - Inosite
  - Glycogen (?)

Subgroup of nitrogen-free organic acids
- Formic acid
- Sarcolactic acid
- Succinic acid
- Oxyglyceric acid (?)

D GROUP OF ORGANOPLASTIC OR ALBUMINOUS SUBSTANCES

Subgroup of nitrogen-containing sulphatid-phosphatids
- Neuroplastin
- Gangliocytin, cytophosphatid- or nuclein-substances

Subgroup of nitrogen-containing sulphatids
- Albumen
- Collagen

E. GROUP OF INORGANIC PRINCIPLES, ACIDS, BASES AND SALTS

These are found in part in the water-extract, in part in combination with many of the before-named constituents.
- Sulphuric acid
- Hydrochloric acid and chlorine in chlorides
- Phosphoric acid
- Carbonic acid

Potassium, Sodium, Ammonium, Calcium, Magnesium, Copper, Iron, Manganese — In compounds forming bases with products obtained; or in compounds with phosphoric acid, and then combined, as phosphates, with these products; or in combination with mineral acids as free mineral salts in the fluids and extracts.

Aluminum, silicic acid, fluorine

SUMMARY OF ANALYSES OF BRAIN

	Gray matter Percent	White matter Percent
Water driven off at 95°	85.270	70.230
Neuroplastine	7.608	8.630
Ether-extract with cephalins, lecithins and cholesterin	1.950	11 497
Cerebrosids, cerebrin acids and myelin	0.424	6.910
Water-extract	0.500	1.403
Inosite	0.193	0.2171
Lactic acid	0.102	0.0456
Phosphoric acid	0.017	
Potassium	0.025	
Sodium	0.092	
Alkalis (as carbonate)		0.1717

OTHER STUDIES OF THE COMPOUNDS PRESENT IN BRAIN

Waldemar Koch and William H. Goodson (1906) give analyses of two fractions of the gray matter, the prefrontal and the motor areas, which do not differ materially in the normal brain, and of the white medullated matter of the corpus callosum, which differs somewhat from them, particularly in the amount of cerebrins. The sciatic nerve differs from the corpus callosum in having considerably more protein and less water, which may be due to a greater amount of connective tissue. The table below gives the analyses together with some for the study of the effects of degeneration of brain and nerve tissue. W. Koch's (1904) analysis of epileptic brain is given in the chapter on metabolism in disease.

ANALYSES OF NORMAL AND DEGENERATED BRAIN AND NERVE TISSUE (Koch and Goodson, 1906) Percent

	Brain (Human)					Sciatic nerve (Human)	Spinal cord (Dog)	
	Prefrontal area		Motor area		Corpus callosum			
	Normal	Degenerated	Normal	Degenerated			Normal	Degenerated
Total solids	17.5	15.2	18.4	17.4	30.0	35.8	31.5	28.4
	Percent of solids							
Simple proteids	25.8	19.1	26.6	12.1	16.7	12.6	18.1	14.9
Nucleoproteids	23.8	37.7	21.0	35.3	11.4	34.9	6.7	12.8
Lecithins	14.8	12.3	12.4	15.0	14.5	7.1	26.4	26.3
Cephalins	8.9	8.5	11.0	15.0	7.6	7.8		
Cerebrins	7.1	7.7	8.6	12.0	17.7	7.2	15.9	15.1
Sulphur compound	5.9	5.6	5.9	6.0	7.3	10.0	5.3	6.4
Extractives	11.0	10.8	10.6	10.0	5.8	5.0	3.7	3.4
Inorganic salts	7.0	6.6	6.0	6.0	2.7	3.6	2.2	2.0

Other single determinations of phosphorus compounds reported by different workers are collected in the following table:

SOME DETERMINATIONS OF BRAIN OR NERVE CONSTITUENTS

Compound and source	Author	Date	Moist substance Percent	Dry substance Percent
Phosphocarnic acid				
Brain, dog	Panella	1903g 1903h	0.2050	0.9037
Brain, lamb	Panella	1903h	0.2142	1.1803
Brain, pig	Panella	1903h	0.2245	1.0044
Brain, calf	Panella	1903h	0.2837	1.3273
Brain, calf, white matter	Panella	1903h	0.3259	
Brain, calf, gray matter	Panella	1903h	0.1917	
Brain, cat	Panella	1903h	0.2871	1.1841
Brain, guinea-pig	Panella	1903h	0.3502	1.6937
Brain, rabbit	Panella	1903h	0.3520	1.5820
Brain, hen	Panella	1903h	0.3316	1.7240
Lecithin				
Sciatic nerve (human)	Chevalier	1886		14.80
Embryo, 62 cm. (cattle)	Raske	1886	0.610	6.6331
Embryo, 68 cm. (cattle)	Raske	1886	0.315	3.4923
Gray matter of brain	Petrowsky	1873	3.1714	17.2402
White matter of brain	Petrowsky	1873	3.1347	9.9045
Whole brain	Burow	1900	3.954	
Nuclein				
Whole brain	Geoghegan [1]	1877-78	0.1390	
			0.1624	
			0.1340	
			0.1368	

[1] Percents computed by compilers.

Special studies of cephalin are reported by Thudichum and Kingzett (1876), W. Koch (1902b, 1903), Cousin (1906), Falk (1908), and by Fränkel, Neubauer and Dimitz (Fränkel and Neubauer, 1909; Fränkel and Dimitz, 1909). Falk says that the cephalin of the peripheral nerves is not the same as that of brain.

He reports on the chemical composition of peripheral nerves. Fränkel (1908, 1909b) describes several brain lipoids, and Argiris (1908) reports quantitative estimations of phosphorus compounds on brains of birds and fish.

Scott (1899) discusses the Nissl granules of nerve cells, which are of nucleoprotein nature and are said to consist of chromatin which has diffused from the nucleus into the cytoplasm. Levene (1903c) gives further discussion of these chromatins, saying that they are compounds of nucleic acid with one or more proteins, or with protein and carbohydrate. He reviews the work on the subject, considering the question of the identity or difference of nucleic acids from different sources. The nucleoprotein which Levene (1899) isolated from brain and analyzed was said to differ from other nucleoproteins in its low phosphorus content, and in having a considerably higher amount of proteins bound to its nuclein. Halliburton's (1894) paper on the proteins of brain we have not seen.

The so-called "protagon," which was once looked upon as the most distinctive component of brain tissue, has been proved to be a mixture, and we have given the history of its study in our chapter on the chemistry of phosphatids. Noll (1899) made a number of determinations of protagon in medullary tissues, and all of the early analyses include it as an item. Rosenheim and Tebb (1909c) find that sphingomyelin, containing 4 percent phosphorus, is the most important component of the so-called protagon.

W. Koch (1907b, 1910a) thought he had evidence of a combination which might be called phosphatid-cerebrosid-sulphatid. Barbieri (1909) describes cerebroin, containing 0.7 percent phosphorus, found chiefly in the gray matter of the brain (ox). It yielded neither glycerin nor sugar. Bethe (1902) reports a cerebrinic phosphoric acid of about 1 percent phosphorus content found in the brain of the horse. Jolly (1898) looked for evidence of phosphorus in the organic portions of brain in some other form than such as yields orthophosphoric acid on simple ashing, but did not find it.

Masuda (1910) reports total phosphorus figures for the three divisions of the brain as in the following table:

TOTAL PHOSPHORUS CONTENT OF THE THREE PARTS OF THE BRAIN
Masuda (1910) Percent P

	Cerebrum	Cerebellum	Mid-brain
Man, tuberculous	0.1838	0.1593	0.2638
Man, gangrene	0.3324	0.2829	0.3497
Cow, healthy	0.2545	0.2760	0.4002
Horse, healthy	0.2813	0.2971	0.3736
Pig, healthy	0.2743	0.2824	0.3480

For total phosphorus determinations on the brain of horse see Baumstark (1885) and Chittenden (1897), pig,—Hart, McCollum and Fuller (1909), sheep,—Kutanin (1910), and pigeon,—Funk (1912a).

For partial separations of the groups of phosphorus compounds in the brain of the horse see Baumstark (1885), and the same for sheep, Chittenden (1897).

DIFFERENTIAL ESTIMATIONS OF PHOSPHORUS COMPOUNDS OF BRAIN UNDER SPECIAL CONDITIONS

In their report of "A Chemical Study of the Brain in Healthy and Diseased Conditions, with Especial Reference to Dementia Praecox," W. Koch and Mann (1909) give the following as the partition of phosphorus among the various classes of compounds. We have brought together all of those which are spoken of as normal and grouped the pathological cases as do the authors. The values are percents of the total phosphorus.

PARTITION OF PHOSPHORUS AMONG THE BRAIN COMPOUNDS
Koch and Mann (1909)

	Total P Percent of solids		Percent of total P					
			Protein P		Lipoid P		Extractive P	
	Part	Whole brain	Part	Whole brain	Part	Whole brain	Part	Whole brain
6-weeks child[1]		1.72		5		54		41
2-yr. child, cortex	1.50		6		62		32	
2-yr. child, corpus callosum	1.46		6		72		22	
2-yr. child, whole by computation		1.48		6		67		27
12yr. child, cortex	1.45		5		63		32	
12-yr. child, corpus callosum	1.45		5		81		15	
12-yr. child, whole by computation		1.45		5		72		23
16-yr., Case 20		...		4.7		70.3		25.1
24-yr., Case 19		1.50		3.7		73.1		23.2
43-yr., Case 70				6		75		19
49-yr., Case 18				3.9		71.8		24.2
Dementia praecox, Case 28				3.8		73.7		22.6
Dementia praecox, Case 29				5.1		73.0		21.9
Dementia praecox, Case 41				3.6		73.6		22.9
Dementia praecox, Case 42				4.7		70.8		24.4
General paralysis, Case 22				5.9		69.3		24.7
General paralysis, Case 23				4.8		70.6		24.7
General paralysis, Case 24				4.6		68.2		26.9
General paralysis, Case 40				4.6		69.9		25.6
Melancholia, Case 25				4.2		69.2		26.6
Melancholia, Case 26				4.1		74.7		21.2
Brain of a dog		1.50		4.5		70.		25.5

[1] Birth premature; brain underdeveloped.

The authors' conclusions with regard to the phosphorus are:— 1. With growth of the brain there is an increase in the lipoid phosphorus and a decrease in the extractive phosphorus. 2. The phosphorus agreement between the brain of man and dog is quite close. 3. Comparison of brains from cases in which the causes of

death were of an entirely different character showed no variations of importance. 4. The brains from cases of dementia praecox showed no marked change in the amount and distribution of phosphorus as compared with the normal. 5. The results from brains of cases of general paralysis show that the destructive changes in this disease affect the brain generally and not one constituent in particular. There is, however, a tendency for the lipoid phosphorus to be decreased, indicating a greater destruction of the phosphatids.

CHANGES OF THE BRAIN WITH GROWTH

Koch and Mann (1907) give the following comparison of the chemical composition of three human brains at different ages, and draw conclusions as quoted:

COMPARISON OF BRAINS OF DIFFERENT AGES—Percents of Solids

	6-weeks child	2-years old			19-years old		
	Whole	Gray	White	Whole	Gray	White	Whole
Proteins	46.6	48.4	31.9	40.1	47.1	27.1	37.1
Extractives	12.0	10.0	5.9	8.0	9.5	3.9	6.7
Ash	8.3	5.8	3.2	4.5	5.9	2.4	4.1
Lecithins and cephalins	24.2	24.7	26.3	25.5	23.7	31.0	27.3
Cerebrins	6.9	8 6	17.2	12.9	8.8	16.6	12.7
Lipoid S as SO_4	0.1	0.1	0.5	0.3	0.1	0.5	0.3
Cholesterin (by difference)	1.9	2.4	15.0	8.7	4.9	18.5	11.7
Moisture	88.78	84.49	76.45	80.47	83.17	69.67	76.42
Total sulphur	0.52	0 53	0.63	0.58	0.46	0.50	0.48
Total P	1.72	1.50	1.64	1.48	1.45	1.45	1.45
DISTRIBUTION OF SULPHUR—Percent of Total Sulphur							
Protein S	62	63	55	59	73	51	62
Lipoid S	6	6	27	17	7	36	22
Neutral S	26	22	13	17	12	6	9
Inorganic S	6	9	5	7	8	7	7
DISTRIBUTION OF PHOSPHORUS—Percent of Total Phosphorus							
Protein P	5	6	6	6	5	5	5
Lipoid P	54	62	72	67	63	81	72
Water-soluble P	41	32	22	27	32	15	23

"In the above table is to be observed with the growth of the brain:

"A decrease in moisture, proteins, extractives, and ash, a change usually found in growing tissues.

"An increase in cerebrins, lipoid sulphur and cholesterin, in other words the substances which predominate in the white matter.

"The relative increase in the lecithin and cephalin is not so apparent, as at an early age the brain is supplied with practically the same proportion of lecithin and cephalin as the adult; in fact, it is the richest tissue in these constituents, the adrenal coming next with 12 percent and the liver with 10 percent.

"In the distribution of phosphorus and sulphur there is to be observed a tendency of the water-soluble forms to become converted into more complex water-insoluble forms, principally lipoids, which increase much more in actual amount than the above increase in relative amount might indicate. The variation in both the protein sulphur and phosphorus is less than might be expected."

M. Cohn (1907) gives the following determinations on the brains of children. No changes were noted as characteristic of the diseases.

ANALYSES OF THE BRAINS OF CHILDREN
M. Cohn (1907)

No.	Age	Sex	Diagnosis	Wt. of brain Grams	H_2O Percent	Percent of dry substance		
						N	P	Ca
1	Fetus, 25 cm.	..	.....	56	91.1	9.44	....	0.0631
2	1 day	..	.....	495	89.30	9.69	1.69	0.0519
3	1½ mos.	M	Intestinal catarrh	402	87.80	9.47	1.64	.....
4	3¾ mos.	F	Naval sepsis	547	86.17	9.76	1.58	0.0231
5	7 mos.	F	Pneumonia	656	83.65	8.95	1.68	0.0285
6	8 mos.	M	Post pneumonia empyema	824	83.35	9.09	1.58	0.0263
7	11 mos.	F	Pneumonia, measles	846	83.93	8.92	1.56	.....
8	1¼ yrs.	F	Pneumonia, measles	801	82.34	9.35	1.62	0.0237
9	2¼ yrs.	F	Pneumonia, measles	994	82.15	8.58	1.55	0.0197
10	3½ yrs.	M	Scarlatina	1247	81.57	8.05	1.51	.....
11	4 yrs.	M	Diphtheria	1304	80.33	7.97	1.50	0.0191
12	6¼ yrs.	F	Scarlatina	1280	80.01	8.15	1.51	0.0181
13	20 yrs.	F	Erysipelas, nephritis	1270	77.52	7.57	1.50	0.0169
14	6½ mos.	M	Tetanus	822?	84.40	9.72	1.71	0.0282
15	10½ mos.	M	Atrophy, tetanus	750	84.31	9.15	1.72	0.0225

Dhéré and Maurice (1909) made analyses of the peripheral nerves of 19 dogs betwen the ages of 4 weeks and 8 years, from which they report the following results, and conclude that the phosphorus content of nerves (on the dry basis) diminishes with increase of age, but the diminution does not occur equally among the different groups of phosphorus compounds.

ANALYSES OF PERIPHERAL NERVES OF DOGS OF DIFFERENT AGES
Dhéré and Maurice (1909)

Group	Ages	No.	Percents of dry substance				Percents of total P		
			Total P	Lipoid P	Nuclein P	Inorganic P	Lipoid P	Nuclein P	Inorganic P
I	4 wks.—4 mos.	9	0.990	0.430	0.072	0.488	43.43	7 27	49.30
II	6—13 mos.	6	0.717	0.335	0.061	0.321	46.72 (gain of 7.6%)	8.51 (gain of 17.0%)	44.77 (loss of 9.2%)
III	2—8 yrs.	4	0.605	0.285	0.056	0.264	47.11 (gain of 8.5%)	9.26 (gain o 27.4%)	43.63 (loss of 11.5%)

See also Kutanin (1910)

J. Smith and W. Mair (1912) give the following report of a study of the lipoid content of the brains of dogs of different ages,—a litter of eight pups and their mother. They find that, while the total lipoids and the cerebrosids show a marked and constant increase with age, the percentage of phosphorus and phosphatids show a maximum at 3 weeks, and thereafter a continuous decrease, although the absolute amount present increases constantly. Attention is called to the fact that while the milk contains only minute traces of these lipoids, in the brain alone at the age of 3 to 6 weeks there is a daily addition of .045 gm. phosphatid, .007 gm. cerebrosid, and .015 gm. cholesterin. This is taken as evidence of a synthesis of the compounds in the body.

LIPOID CONTENT OF DOGS' BRAINS AT DIFFERENT AGES
Smith and Mair (1912)

Age and subject	3 days, 3 dogs	3 weeks, 3 dogs	6 weeks, 1 dog	12 weeks, 1 dog	Adult, 1 dog	Human adult
Dried brain, gms.	1.38	5.40	8.90	15.0	19.25	....
Extract, percent	23	25	34	38	47	....
Percentage Composition of Chloroform Extract						
Cholesterin	18.3	16.8	18.5	17.1	21.8	21.8
Cerebrosid	1.5	3.5	6.8	11.5	21.4	10.7
Phosphorus	2.10	2.42	2.27	2.11	1.76	1.58
Phosphatid	52.	60.	57.	52.	44.	39.5
Other lipoids	28.	20.	28.	19.	13.	28.
Amounts Found in the Brain—Grams						
Phosphatid	0.16	0.80	1.70	2.90	4.0	
Cerebrosid	0.005	0.046	0.20	0 67	1.95	
Cholesterin	0.058	0.22	0.55	1.00	2.0	
Other lipoids	0.10	0.28	0.55	1.20	1.17	
Total extract	0.32	1.34	3.00	5.77	9.12	

Messing (1912) studied the mineral constituents of normal and pathological brains. The P_2O_5 content increases with age and the weight of the brain, until about the 60th year, after which it decreases. Arteriosclerosis causes a decrease of the phosphorus, and an increase of both calcium and SO_3.

Mathilde Koch (1913) has made similar determinations to those of Koch and Mann on brains from pig fetuses of 50, 100 and 200 mm. length, and from albino rats at birth, and in the adult state, carrying on work started by Waldemar Koch. She finds that chemically, anatomically and physiologically, the brain of the albino rat is at about the same stage at birth that the pig fetus is at 50 or 100 mm., and represents as young nervous material as can conveniently be analyzed at present. The phosphatids there comprise 15.2 percent of the solids, and the total phosphorus 1.87 percent. Of the phosphorus 13.3 percent is in protein, 33.1 percent in lipoid and 53.55

percent in water-soluble form. From examinations of rat brains at 1, 10, 20, 40, 120 and 210 days (Koch, W., and M. L., 1913) it is learned, among other things, that in the period of the most rapid growth and of the beginning of medullation, from the 10th to the 20th day, there is most rapid development of phosphatids. Phosphatids are found in both cells and sheaths.

PHOSPHORUS IN THE LIVER

Phosphorus Content. Szymkiewicz (1891) made sulphur and phosphorus determinations on the ash of some 80 samples of the livers of cattle of various ages, from the 13-cm. fetus to the cow of 13 years. In the cases of the smaller fetuses a mixture of 2-6 livers was used. There were no characteristic variations in the phosphorus content of the livers of the fetuses (minimum, 1.52 and maximum, 1.98 percent), though there were irregular individual variations. As a rule the phosphorus content after birth is appreciably lower than before birth, although among the 24 there were some individual cases in which the phosphorus content is higher than the lowest found in the fetus. Among the 24 there is no evidence of any characteristic effect due to advancing age or to sex. The mean of the values on calves, oxen and cows is 1.39 percent P.

Krüger (1895) obtained results practically like those of Szymkiewicz except that his averages for adult animals are somewhat lower than for calves. In the livers from human subjects the phosphorus was considerably higher in the new-born infants than in the adults.

AVERAGE PHOSPHORUS (P) CONTENT OF LIVERS OF CATTLE OF DIFFERENT AGES (Friedrich Krüger, 1895) Percent Dry Basis

Fetuses, length in centimeters						Calves	Cows	Oxen
30-40	40-50	50-60	60-70	70-80	80-90 90-100			
1.74	1.73	1.73	1.65	1.69	1.72	1.46	1.29	1.30

Weiske's (1886) experiment testing the effects on lambs of feeding hay which had been treated with dilute sulphuric acid showed the phosphorus content of the livers of the 3 lambs on such feed and on normal feed to range between 0.450 and 0. 485 percent P, with the mean value of 0.468 percent.

Paton (1895-6), in discussing the relation of the liver to the metabolism of fat, submits the following lecithin determinations on the livers of animals under known conditions of feeding. The *amount* of lecithin in the liver appeared to be somewhat nearly constant, its considerable percentage variations being due in large part to the storage or removal of fat, as determined by the general state of nutrition of the animal.

CONTENT OF LECITHIN IN LIVER OF VARIOUS ANIMALS UNDER DIFFERENT CONDITIONS OF FEEDING—Paton (1895-96)

Animal	Lecithin			Feed
	Percent of liver	Percent of solids of liver	Percent of ether extract of liver	
Rabbit	2.60	11.4	56.1	Bran and oats
Rabbit	2.70	11.9	58.4	" " "
Rabbit	2.05		51.3	Bran and green food
Cat	1.90		36.4	
Kitten	2.57	9.1	50.0	Bread and milk
Kitten	3.04	10.3	60.0	Fast of 48 hours
Kitten	3.31	11.7	70.0	" " 59 "
Kitten	1.72	5.2	11.0	Twenty-four hours after cream
Kitten	1.42	9.8	3.53	Cream diet for weeks
Rabbit, very fat	2.24	8.9	34.2	Turnips

Balthazard (1901a) investigated the lecithin content of the liver in a number of cases of different diseases or artificially produced pathological conditions in animals. He found the lecithin high in all the pathological cases examined; thus it was increased by infection in tuberculosis and diphtheria, by intoxication with a mineral poison, phosphorus; by bacterial poison—typhus toxin, or by autointoxication, as in inanition and uremia. Balthazard concluded that a large part of the hepatic lecithin comes from the destruction of leucocytes of the circulating blood.

The livers of 4 pigs to which Hart, McCollum and Fuller (1909) had given different amounts and different kinds of phosphorus in the diet showed a phosphorus content of from 1.27 to 1.43 percent P in the air-dry substance, with an average of 1.35 percent.

Forbes (1909) found the phosphorus of the livers of pigs to vary between 0.291 and 0.367 percent, and the phosphorus in the ash between 24.18 and 28.23 percent, as affected by the food received.

The bile and liver of cattle were analyzed by Daniel-Brunet and Rolland (1911b) and the phosphate content of liver showed a range from 2.90 to 3.48 parts P_2O_5 per 1000 parts fresh substance (1.26-1.52 parts P).

For phosphorus estimations in the liver in various pathological states see Robin (1911).

Partition of the Phosphorus in Liver. Plósz (1873) identified nuclein in liver, and A. Kossel (1882) submitted the following figures for nuclein phosphorus in liver.

TOTAL PHOSPHORUS AND NUCLEIN PHOSPHORUS IN LIVER
Kossel (1882)—Percent

Species	H_3PO_4 in fresh organ	Nuclein H_3PO_4	Nuclein H_3PO_4 in total H_3PO_4
Dog	0.846	0.444	52.5
Cattle	1.267	0.390	30.8
Hen, fasted	1.077	0.511	47.4
Hen, well fed	0.834	0.264	31.7

Drechsel (1886) showed that jecorin is found in liver. Paul Manasse (1895) isolated from the liver of the horse a phosphatid which yielded grape sugar on cleavage and hence was supposed to be jecorin. Waldvogel and Tintemann (1906) also report jecorin in the liver. Baskoff (1908) found in addition to lecithin and jecorin another phosphatid which he named heparphosphatid. Kennaway and Leathes (1909) found the jecorin fraction of the lipoids from the liver of the pig higher in phosphorus than that from the liver of the dog or the goat.

The compounds which Liebermann (1893a) studied and called lecithalbumins were found in most abundance in liver and lungs. Phosphocarnic acid is reported by Siegfried (1896) and by Balke and Ide (1896). Balke and Ide give the amount as 0.183 percent in the liver of the dog and 0.015 percent in that of the horse. Levene and Mandel (1908b) say that among the nucleic acids is guanylic acid, and others describe a ferruginous nucleoprotein, or mixture of such nucleoproteins, to which the name "ferratin" is given.

Masing (1911b) published a series of analyses which indicate a percentage decrease in amount of nucleic acid in the rabbit and in rabbit livers with advancing stages of development, both before and after birth.

NUCLEIN-PHOSPHORUS IN RABBIT EMBRYOS AND RABBIT LIVERS
Masing (1911)

Stage of development	Average weight of animal Grams	Nuclein P of whole animal for 0.35 gm. N Milligrams	Average weight of liver Grams	Nuclein P of liver for 0.35 gm. N. Milligrams
18 embryos 0.5–1.5 cm. long from 1st half of gestation; total N about 21 mg.	...	20.3	...	...
2 embryos averaging 21.5 gm. in weight; about the beginning of the 4th week of gestation	21.5	17.8	2	22.8
1 embryo at same stage as the last; considerably less N	22.5	17.	...	...
2 embryos somewhat older	28.	14.7	...	...
5 livers from stage somewhat later than the other livers	28	...	1.8	20.4
4 embryos (5 livers) about 1-2 days before birth	36	13.	2.6	18.0
2 embryos, mature	43	12.	...	...
Young just after birth (small breed; 4 livers)	33	11.7	2.3	17.
11 days old animal (skin and stomach contents removed)	57	11.9	...	...
2 livers of 11 days old animals	72	...	4.0	16.
2 livers of 22 days old animals	210	...	9.5	12
Liver of a full-grown animal	1800	...	65.	11.5
Ditto	...	...	...	10.

Scaffidi (1908) made nucleoprotein determinations on the livers of rabbits in connection with his study of the iron distribution in the liver after feeding an iron paranucleinate called "triferrin," This paranucleinate did not affect either the nucleoprotein content of the liver or the phosphorus content of the nucleoprotein, as it did apparently the iron. The amounts of nucleoprotein found in the livers of the several rabbits range from 0.3595 to 1.2334 percent of the liver, and the phosphorus content of the nucleoprotein from 2.51 to 2.83 percent, while the iron content of the nucleoprotein in the control animals ranged from 0.18 to 0.44 percent, averaging 0.30 percent, and that of the experiment animals from 0.34 to 1.10 percent, averaging 0.67 percent.

PHOSPHORUS IN SPLEEN

Phosphorus Content. Krüger (1895) examined spleens and livers of cattle fetuses, calves and adults. The phosphorus content of the spleen was found to be highest when the fetus was 30-60 cm. in length, and lowest in the adult animal. In the adults, livers and spleens gave about the same figure.

AVERAGE PHOSPHORUS (P) CONTENT OF THE SPLEEN OF CATTLE OF DIFFERENT AGES (Krüger, 1895)—Percent Dry Basis

Fetuses, length in centimeters							Calves	Cows	Oxen
30-40	40-50	50-60	60-70	70-80	80-90	90-100			
2.38	2.43	2.39	2.13	1.94	1.70	1.48	1 .82	1.26	1.37

Dhéré and Maurice (1910) find a steady decrease of phosphorus in the spleen of dogs with advancing age.

INFLUENCE OF AGE ON THE QUANTITY AND PARTITION OF PHOSPHORUS IN THE SPLEEN OF DOGS
Dhéré and Maurice (1910)

Age	Number of dogs	Phosphorus, percent of fresh substance	Phosphorus, percent of dry substance	Percent of total phosphorus		
				Lipoid	Nucleic	Inorganic
Few hours to 15 days.	21	0.35	1.70	13.55	8.67	77.78
4 weeks to 4 months.....	9	0.34	1.61	16.75	7.85	75.40
6 months to 15 months..... . .	6	0.29	1.32	16.91	6.57	76.52
2 years to 8 years.....	4	0.25	1.09	21.17	11.05	67.78

Partition of the Phosphorus of Spleen. A. Kossel (1882) submitted the following figures for total and nuclein phosphorus in spleen.

TOTAL AND NUCLEIN PHOSPHORUS IN SPLEEN—(Kossel, 1882) Percent

Species	H_3PO_4 in fresh organ	Nuclein H_3PO_4	Nuclein H_3PO_4 in total H_3PO_4	
Horse	1.162	0.867	74.6	
Horse	0.837	0.593	70.9	
Cattle	1.005	0.636	63.3	} Duplicates
Cattle	....	0.676	67.3	

Liebermann (1893a) found considerable of lecithalbumin in spleen. Gourlay (1894) isolated from spleen a substance he called nucleoalbumin. Phosphocarnic acid, phosphatids and nucleoproteins are found. Besides the jecorin (Waldvogel and Tintemann, 1906), which is free from iron, Burow (1910) found three iron-containing phosphatids in the spleens of cattle and of men. The presence of iron in the lipoids of spleen is considered significant in connection with the view that the chief physiological function of the spleen, aside from leucocyte formation, may be iron metabolism. Capezzuoli (1909a) found considerable iron in the nucleoprotein. According to Sato (1909), the iron of the nucleoprotein is present in two forms, one more stable than the other.

Sato (1909) obtained 0.709, 0.406, 0.481, and 0.498 percent nucleoprotein from the spleens of cattle. Corper (1912) reports that the spleen of the dog contains 6-7 percent lecithin; about 0.27-0.52 percent water-soluble phosphorus and about 0.39 percent insoluble phosphorus.

Panella (1904c) made water and nucleon determinations on the fresh spleen of cattle, horses, sheep, swine and dogs, and found it present in all in amounts varying somewhat with the species. The nucleon content of the spleen of cattle, sheep and dogs seems to decrease with increasing years.

The values found are as follows:

WATER AND NUCLEON CONTENT OF FRESH SPLEEN—Percent

Animal	Water	Nucleon	
		Fresh subs.	Dry subs.
Cattle	78 88	0.31	1.46
Horse	78 64	0 36	1.17
Sheep	77.27	0.40	1 76
Swine	78 92	0.57	2.70
Dogs	78.79	0.67	3.16

PHOSPHORUS IN THE PANCREAS

Phosphorus Content. Lüning (1899) reports the phosphoric acid of the ash of the pancreas of two aged women as 46.99 and 45.29 percent, respectively. See also Gossmann (1898) and Juchler (1912).

Juchler (1913) found phosphorus in the pancreas of adults in amounts varying within narrow limits, apparently mainly in organic condition. The percentage of total P_2O_5 in the fresh pancreas at various ages is as follows: New-born 2.36; 7 mos.-5 years 1.03; 20 years-48 years 0.55; 50 or more years 0.42; adults in general 0.48.

Partition of the Phosphorus. Fränkel, Linnert and Pari (Fränkel and Pari, 1909; Fränkel, Linnert and Pari, 1909) have made a special study of a phosphatid found in the pancreas of cattle.

Plimmer and Kaja (1909) show that a prominent feature in the phosphorus changes in the pancreas, accompanying the secretion of pancreatic juice, is the destruction of phosphoprotein, which decreases from about 2.5 percent of the total phosphorus to less than half of one percent of the total phosphorus. The total phosphorus of the pancreatic juice is very small in amount. Its total protein phosphorus is phosphoprotein, and inorganic phosphorus is also present. It contains no lecithin. Below are the analytical data on this matter.

PHOSPHORUS (P_2O_5) CONSTITUENTS OF PANCREAS AND PANCREATIC JUICE—Percent

Condition of Phosphorus	Dog's pancreas, normal				Dog's pancreas after action of secretin			Pancreatic juice of dog		
	I	II	III	IV	I	II	III	I	II	III
Ether soluble (lecithin) ...	8.6	28.5	30.6	28.6	31.1	28.0	31.0	0.0	0.0	0.0
Water soluble (nucleic acid+ inorganic) ..	37 6	15.5	17.4	14.4	16 2	19.8	16.2	56.3	86 3	59.8
Inorganic	16.4	7.1	7.8	6.4	7.3	6.9	6.7	present	trace	trace
Protein (nucleoprotein+phosphoprotein) .	53.8	56.0	52.0	57.0	52.7	52.2	52.8	43.7	13.7	36.7
Phosphoprotein .	2 5	2.6	1 6	1.9	0.4	0.3	0.0	43.7	13.7	40.2

A. Kossel (1882) reports the total phosphorus (H_3PO_4) of the pancreas of cattle as 1.257 and 1.215 percent, the nuclein phosphorus 0.580 and 0.606 percent, and the percent of nuclein phosphorus in the total phosphorus as 46.1 and 49.9 percent. These pairs of figures are duplicate determinations.

PHOSPHORUS IN KIDNEY

Phosphorus Content. From Gossmann (1898) we compute the percentages of phosphoric acid in the kidneys of man and steer, as follows: man 0.107 percent; steer 0.401 percent.

Forbes (1909) found in the kidneys of swine phosphorus varying between 0.205 and 0.318 percent and in the ash 18.47-27.90 percent.

Partition of the Phosphorus. A. Kossel (1882) found in bovine kidney 0.7584 percent H_3PO_4, 0.285 percent nuclein H_3PO_4 and 37.6 percent nuclein P in the total P.

Lönnberg (1890) reports finding nucleoalbumins in the cortical substance and the medullary substance of kidney, and in the mucous membrane of the urinary bladder. Liebermann (1891b, 1893a, 1893b) found in the parenchyma of the kidney a compound which he called lecithalbumin, and which, after removal, had such properties as to suggest that in the tissues it might be the agent by which the kidney excretes acid urine from alkaline blood. The substance in the kidneys which others had called protagon Panzer (1906) states to be a cholesterol compound not containing phosphorus. Balke and Ide (1896) obtained 0.043 percent phosphocarnic acid from the kidney of the horse and 0.205 percent from that of the dog. Lusena (1903) gives the lecithin content of the kidneys of rabbits as averaging 2.086 percent for the normal organs and 1.856 for organs affected by experimental fatty degeneration. Rubow (1905) reported the following lecithin phosphorus figures for the kidneys of dogs in various conditions.

LECITHIN AND FAT CONTENT OF THE KIDNEYS OF DOGS
Rubow (1905) Percent, Fresh Basis

Condition of dog	Kidney	Ether extract	Lecithin	Fat
Normal, well fed, I	Right	13.81		
	Left	13.63		
Normal, well fed, II	Right	15.21		
	Left	14.99		
Normal, well fed, III	Right extirpated	19.46	6.60	12.86
	Left	21.28	6.86	14.42
Normal, well fed, IV	Left extirpated	14.06	8.66	5.40
	Right	14.97	8.63	6.34
Fasted 19 days		15.04	7.57	7.47
Fasted 22 days		15.74	7.95	7.79
Phosphorus-poisoned, about 3 mg. per kg. body weight, injected	Left extirpated	13.61	7.87	5.74
	Right	13.13	7.39	5.74
Phosphorus-poisoned, about 3 mg. per kg. body weight, injected	Left extirpated	15.65	8.55	7.10
	Right	15.79	8.32	7.47
Under chloroform for 5 hrs. two days before death		12.49	7.89	4.60
Under chloroform for 5 hrs. two days before death		15.33	7.90	7.43

Dunham (1903-4, 1904-05, 1905-06, 1908) and Dunham and Jacobson (1910) isolated and studied a peculiar phosphatid found in the kidneys of cattle, which they call "carnaubon." Fränkel and Nogueira (1909a, 1909b) describe three unsaturated phosphatids. MacLean (1912a, 1912b, 1912-13) has made painstaking examinations of the phosphatids of the kidney of the horse and finds the chief one to be a lecithin, or at least a phosphatid having the N:P relation 1:1. He finds also cuorin and a diamino-monophosphatid which he considers as probably the carnaubon of Dunham and Jacobson freed from a nitrogenous impurity present in their product.

PHOSPHORUS IN SUPRARENAL CAPSULES

Paul Manasse (1895) isolated from the adrenals of the horse and of cattle a sugar-yielding phosphatid supposed to be jecorin. Orgler (1904) reports a substance similar to the so-called protagon of the brain (0.6 percent of the substance), and Rosenheim and Tebb (1909b) found in the adrenals a small amount of the sphingomyelin such as they consider a prominent constituent of the protagon of brain.

Bernard, Bigart and Labbé (1903a, 1903b) identified as lecithin, or a mixture of lecithins, the distinctive fat occurring in the spongiocytes of the suprarenal capsules and increasing during the functioning of the organs. It is looked upon as a secretion of these cells. The phosphorized fat was found to be in the horse 45.3 percent, in the sheep 48.8 percent, in the rabbit 52.7 percent and in man (one case) 13.1 percent of the total fat of the organ. The total amount found was in the horse 6.77 percent of the gland and in man 2.08 percent.

The following are Alexander's (1892) determinations of the lecithin and the nuclein phosphoric acid.

LECITHIN AND NUCLEIN PHOSPHORIC ACID DETERMINATIONS ON THE ADRENALS OF THE HORSE (Carl Alexander, 1892)

Age of horse	Lecithin		Nuclein phosphoric acid	
	Percent of fresh substance	Percent of dry substance	H_3PO_4, percent of fresh substance	H_3PO_4, percent of dry substance
16 years..	4.2973	26.018	.....	....
3 years..	2.81383	16 6114	0.7781	4.592
2 years..	2.573	16.071	.....	....
2 years..	3.4502	21.964	.....	....

PHOSPHORUS IN THE THYMUS

Lilienfeld (1894) reports a general chemical examination of leucocytes from the thymus of calves. He found a nucleoprotein, protagon, inosite, monopotassium phosphate, lecithin and nucleohistone. The total phosphorus is given as 3.01 percent of the dry substance, the lecithin as 7.51 percent and the nuclein as 68.78 percent.

Huiskamp (1901a) says that 69.4 percent of the proteins of the thymus are in nucleohistone and 18.7 percent in nucleoprotein, leaving only 11.9 percent of other proteins. Malengreau (1900, 1901) states that there are two nucleoalbumins and two histones in the thymus. Herlitzka and Borrino (1902, 1902b, 1903) try to distinguish the parts played by the nucleohistones and the nucleoproteins of the thymus, the liver and the kidney.

The nucleohistone of the thymus has been given considerable attention. (See Lilienfeld, 1894, 1895; Bang, 1900a, 1900b; Kossel, A., 1900; Malengreau, 1901; Huiskamp, 1901a, 1901b, 1903; Herlitzka and Borrino, 1902a, 1902b, 1903). A nucleohistone is a nucleoprotein in which the nucleic acid is united with one of the simple proteins, a histone. The result is a nucleoprotein differing from most of the members of this group through the content of a larger proportion of nucleic acid and relatively little protein. According to Goubau (1911) it is characteristic of little-differentiated cells. There seems to be present in the thymus at least one nucleoprotein of this type and one of the type containing relatively less nucleic acid. It will be observed that a very large proportion of the proteins of this gland are united with phosphorus in one or the other of these ways. Goubau finds nucleohistone much more abundant in thymus than in any other mammalian organs, and says that this nucleohistone of the thymus is of a different type from that of the other organs; it is insoluble in physiological salt solution. It is not found in human or horse serum nor in ascitic fluid containing bile. It is probable that the histones and nucleohistones are fixed in such organs as the thymus and the spleen, and hence cannot be carried away in body fluids.

PHOSPHORUS IN THE THYROID

According to Gourlay (1894), the only protein of the thyroid is a nucleoalbumin which, from microchemical examination, he concluded is derived, at least in part, from the colloid matter of the acini.

Baldoni (1899-1900) gives these phosphorus and nucleoprotein determinations on thyroids of different animals.

ANALYSES OF THYROID GLANDS—(Baldoni, 1900) Percent

Species	Water	Ash	P_2O_5 in ash	P_2O_5 in fresh substance*	Nucleoprotein in dry substance*	Nucleoprotein in fresh substance
Swine	68.09	0.92	12.59	0.116	5.55	1.771
Cattle (Tuscan)	74.71	0.74	23.24	0.172	3.49	0.883
Cattle (Maremma)	69.79	1.00	12.48	0.125	4.15	1.254
Buffalo	70.81	1.03	13.59	0.140	3.43	1.001
Sheep	73.30	0.92	14.66	0.135	3.69	0.985
Horse	73.79	0.98	16.31	0.160	4.45	1.166

* Computed by F. & K.

Markotum (1895) describes from the thyroid of cattle a phosphorus-containing substance "thyreonucleoalbumin," which is said to have the following composition: C 51.46, N 15.56, H 6.94, P 0.32, S 1.5 and O 24.12. Markotum says that the alteration of the nervous system by the thyroid is supposed to be through this compound.

Oswald (1899) finds that the active agent of the thyroid gland as used in pathological cases, the so-called thyroid gland colloid, is a mixture of two compounds. The iodine-containing body, thyreoglobulin, which was shown to have the characteristic influence on nitrogen metabolism when the gland was administered to dogs, is free from phosphorus; but it is associated in the colloid with a small amount of nucleoprotein containing 0.16 percent phosphorus.

Fenger (1913), in connection with an extensive study of the iodine content of the thyroid glands of animals in both the adult and the fetal stage, has found with regard to cattle that "enlarged glands in general, both fetal and adult, contain less total iodine and much more total phosphorus than normal thyroids," and that "normal fetal glands are relatively larger and contain more iodine and phosphorus per unit of body weight than thyroids from fully mature animals."

In a later paper Fenger (1914) reported studies on the composition of the thyroid gland in cattle as affected by sex and pregnancy. Among his conclusions are the following:

"Castrated males contain less thyroid tissue than either uncastrated males or females, but the iodine content per unit of body weight is about half-way between the uncastrated male and female animals.

"The phosphorus content of the thyroid gland seems to be fairly uniform in all four cases and should only be considered as indication of normal physiological activity."

From the analytical data we select the following:

PHOSPHORUS AND IODINE CONTENT OF THYROID GLAND OF CATTLE

	Phosphorus in fresh gland Mg.	Iodine in fresh gland Mg.	Fresh gland tissue per 100 lbs. body weight Grams	Phosphorus per 100 lbs. body weight Mg.	Iodine per 100 lbs. body weight Mg.
Bulls	30.66	19.38	2 14	2.19	1 38
Steers	23.97	19.73	1.92	2.00	1 64
Pregnant cows	21.08	18.50	2.44	2.11	1.85
Non-pregnant cows and heifers..	20.52	16.98	2 44	2.22	1.84

PHOSPHORUS IN THE LUNGS

By Sieber and Dzierzgowski (1909) the mixed lung tissue of several horses was found to contain 76.6 percent water, and of the dry substance 1.107 percent was phosphorus; which equals 0.259 percent in the fresh substance.

The compounds which Liebermann (1893a) studied and called lecithalbumins were found abundant in lungs. According to Sieber (1909b), the phosphatid extract of lungs (horse) includes lecithin and jecorin in the approximate proportion 6:1. A cholesterol-like substance was also isolated. There is a discussion by Zoja (1894) on the lecithin of the alveolar cells of the lungs and the semeiological significance of the myelin drops of the sputum.

PHOSPHORUS IN THE HYPOPHYSIS

According to the analyses of Malcolm (1904), the pituitary gland contains in its "glandular portion" 0.72 percent P and in its "nervous portion" 0.8 percent.

PHOSPHORUS IN THE DIGESTIVE MUCOSA

After peptic digestion of the mucous membrane of the stomach, Liebermann (1891a) obtained a lecithin-albumin complex which he thought existed as such in the walls of the stomach and there functioned significantly in the control of stomach acidity.

Borri (1906) studied the phosphorus compounds of the mucous membrane of the intestine (dog), distinguishing nucleoprotein, phosphorized fats, lecithalbumin and perhaps some other phosphorized organic body as well as inorganic phosphate. He says that there are no nucleoalbumins present. The phosphate content of a water extract of the membrane was distinctly less after fast. The ingestion of oleic acid after a three-days' fast increased the phosphate content of the extract, which is interpreted as supporting the idea that glycerin to unite with the fatty acid was obtained from the lecithalbumin of the membrane.

Araki (1903b) isolated nucleic acid from the mucous membrane of the small intestine to the extent of 0.66 percent.

PHOSPHORUS IN THE GENITALIA

Paton and his associates (Paton, 1898; Paton, et al., 1897-98), in their extensive study of the metabolism of salmon in fresh water, gave considerable attention to the forms and amounts of phosphorus present in the genitalia and muscles of salmon at the time of leaving the sea in May, and again in October after the long fast in fresh water, during which time the reproductive organs and products mature. The muscles were shown to have the phosphorus most largely present as inorganic phosphates, while the ovaries had greater amounts of lecithin and of phosphoprotein (ichthulin), and the testes had more than a half of it as nuclein. The muscles lose phosphorus while the genitalia gain it. The following are given as representative figures showing the distribution of phosphorus in each of the three classes of tissue.

DISTRIBUTION OF PHOSPHORUS IN THE MUSCLES AND GENITALIA OF SALMON (Paton, 1897-98)—Percent

Tissue	No. of fish	In ether extract (lecithin)	In water extract (inorganic phosphates	In residue (nucleins or pseudo-nucleins)	Total	
Muscle, thick..	14	0.0416	0.131	0.056	0.228	Estuary fish
Muscle, thin...	14	0.0460	0.094	0.041	0.181	The "thin" muscle is said to make up about ¼ of the body
Muscle, thick..	76	0.060	0.095	0.055	0.210	Estuary fish taken later in the year
Muscle, thin...	76	0.060	0.119	0.063	0.242	
Ovary.....	14	0.114	0.057	0.114	0.285	
Ovary.....	76	0.150	0.075	0.189	0.414	
Testis.....	53	0.063	0.068	0.161	0.292	
Testis.....	68	0.060	0.040	0.178	0.278	

Milroy (1908) has since made a similar study of herring. The percentage content of phosphorus (P_2O_5) in ovaries, and the weights of phosphorus per average fish found in these organs are averaged for the months of the year as follows:

PHOSPHORUS (P_2O_5) IN GENITALIA OF THE HERRING—(Milroy, 1908)

	Condition	July Immature	Sept. Ditto	Oct. A Ditto	Oct. B Ditto	Nov. Almost mature	Dec. A Mature	Dec. B Spawning	Jan. A Ditto	Feb. Spent
Ovaries	P_2O_5, percent	0 77	1.23	0.71	0.93	0.91	1.03	1.19	0.93	0.91
	P_2O_5, per fish	0.003	0.011	0.01	0.05	0.26	0.48	0.34	0.16	0.016
Testes	P_2O_5, percent			0.86			2.10			
	P_2O_5, per fish			0.20			1.21			

Plimmer and his associates (Plimmer and Scott, 1908; Plimmer and Kaya, 1909), in their study of the distribution of phosphoproteins in animal products, found them chiefly in milk, egg-yolk and the ova of fish; but they were present also, in smaller proportions, in the pancreas and salivary glands. They do not appear in the thymus nor in the testes of the bull or the codfish. Determinations were made also of the proportionate amounts of the different kinds of phosphorus compounds in the testes of codfish and in the eggs of the frog.

DISTRIBUTION OF PHOSPHORUS IN CERTAIN TISSUES

Plimmer and Kaya (1909)—Percent of Total P_2O_5

Substance examined	Animal	Ether soluble (lecithin)	Water soluble (nucleic acid and inorganic)	Inorganic	Protein (nucleo-protein and phospho-protein)	Phospho-protein
Testes.	Codfish	17.8	22.6	20.5	59.6	0
Testes	Codfish	8.9	31.9	20.4	59.2	0
Eggs, ovarian....	Frog	26.2	4.3	0	69.5	61.9
Eggs, soon after being laid	Frog	19.1	13.0	Trace	67.9	41.1
Eggs, soon after being laid	Frog	21.4	9.6	Trace	69.0	40.9

Panella (1903d, 1903i, 1904a) found, of phosphocarnic acid, 1.1733 percent in the dry testicular substance of the ass, and 0.871 percent in that of the horse.

Konig and Grossfeld (1913a), in considering the food value of fish sperm mention the high phosphorus content (4.46 percent of the ash-free, dry substance of herring sperm and 3.74 percent of that of carp sperm), and the high content of lecithin (20.7 percent of the fat of herring sperm and 20.2 percent of that of carp sperm). In a second article (1913b) they report the phosphorus content of the ichthulin and albumin and the lecithin content of the fat of the roe of several species of fish. The dry, ash-free ichthulin from herring roe contains 1.56 percent and the albumin 1.05 percent phosphorus, while the lecithin content of the fat of herring roe was reported as 43.61 percent.

Rosenbloom (1913a) reports determinations of the percentages of lipins, phospholipins, neutral fat, fatty acids and cholesterol in the ovary and corpus luteum of the cow in the non-pregnant state, and in the pregnant state. The results indicate that there is practically no increase in the above substances during pregnancy in the cow. The phospholipins amount to 3.94 percent of the dry substance in the non-pregnant ovary and 3.48 and 3.63 percent at two stages of pregnancy; those of the non-pregnant corpus luteum were 14.10 percent, and of the pregnant, 14.90 and 14.87 percent of the dry substance.

Bienenfeld (1912), Ballerini (1912) and Sakaki (1912, 1913a, b, c and d) have reported special lipoid studies on the placenta. Sakaki isolated two phosphatids, sphingomyelin and jecorin.

Spermatozoa heads, being mainly nucleus, are composed largely of nucleic acid, and this is, in the case of several fish at least, combined with protamin or histone in a compound more simple than most nucleoproteins of the animal body or its products. This relation has been especially studied by Miescher (1878, 1896, 1897) and by Mathews (1897). The heads are apparently free from lipoids, but the tails contain considerable amounts, and largely as a phosphatid which is reported as lecithin. Gobley (1850b) also found the lecithin here. Mathews reports that jecorin is not present. The ash of spermatozoa is said to be mainly (three quarters) potassium phosphate. The seminal fluid contains nucleon, and its mineral matter is chiefly calcium phosphate and sodium chloride.

Percival (1902) made phosphorus studies on a number of animal organs. The total phosphorus figures on the oxidized tissue are as follows, being given as percent of P_2O_5 in the fresh substance, and arranged in order of decreasing amount of phosphorus: Thymus 1.223; heart (sheep) 1.011; pancreas (sheep) 0.749; lung (sheep) 0.745; brain (sheep) 0.635; spleen (beef) 0.570; liver (beef) 0.561; testicles of calf 0.517; muscles (beef) 0.506; testicles of bull 0.470; kidney (sheep) 0.454; ovary (cow) 0.429; udder (cow) 0.414; thyroids (sheep) 0.369.

For the phosphorus content of the ether extract of many glandular organs see Gérard and Verhaeghe (1911).

PHOSPHORUS OF THE BLOOD

Kinds of Phosphorus Compounds Present. The blood was, naturally, early recognized as an important part of the animal organism the chemical composition of which might be of great significance. In some cases the blood was ashed, and determinations of mineral constituents made on the ash; but in other cases the individual organic constituents were noted. Ash analyses are not very enlightening, and quantitative determinations of the individual compounds cannot be interpreted with definiteness unless the corpuscles and serum be examined separately.

Phosphorus is present as inorganic salts, chiefly potassium phosphate and calcium phosphate, and in organic combination as phosphatids and nucleoproteins or nucleins, and, according to Panella, as phosphocarnic acid.

In 1851 Gobley (1851) found lecithin in blood. "Protagon" studies were reported by both Herrmann (1866) and Hoppe-Seyler (1866a). One of the first findings of nucleoprotein was in blood corpuscles (Plósz, 1871). Pribram (1871) made phosphorus and calcium determinations which distinguished between the amounts precipitable directly from the defibrinated and centrifuged blood serum and that obtained in precipitable form after ashing, or, as it may be interpreted, between the calcium and phosphorus present in inorganic form and the total present. The indication was that none of the calcium was in organic union, while more than two-thirds of the phosphorus was in such a form. Fokker (1873) reported finding calcium acid phosphate bound to protein in the blood serum of the ox.

Nucleoprotein is found in the blood plasma and the serum as well as in the corpuscles; of leucocytes it forms the chief constituent. (See Plósz, 1871; A. Kossel, 1881, 1893; Halliburton and Friend, 1889; Halliburton, 1895; Lilienfeld, 1894; Pekelharing, 1895; Bang, 1903, 1904; and Liebermeister, 1906).

The amount of phosphocarnic acid was studied by Panella (1902c). He found an average of 0.3631 percent in the blood of dogs, 0.282 percent in the blood of rabbits and 0.0674 percent in the blood of calves.

The most frequently quoted early analyses of the blood of different species, including human subjects in different conditions, are those of Becquerel and Rodier (1844), Jüdell (1868), von Bunge (1876), Jarisch (1877) and Miroczkowski (1878).

We have selected from the data of a number of authors items showing the amounts in the blood, of the different phosphorus compounds, and of a few other constituents which may be considered in connection with the same. Some of these are given in connection with studies on the changes brought about in pathological conditions, and are included in the tables with such pathological data. The following table of Abderhalden's is quite unusual with regard to the number of species considered and the completeness and care with which the analyses were made.

Abderhalden has tabulated these analyses to show the amounts of the individual constituents contained in 1000 parts by weight of blood, in 1000 parts of serum and in 1000 parts of corpuscles. He calls attention to the similarity of composition of the serum from the different animals, and the great similarities of composition of the blood of two animals of the same species. It is also very evident that the bloods of the three kinds of ruminants (cattle, sheep and goat) agree much more closely with each other than with that of the carnivora (dog and cat) or with that of the horse, pig and rabbit. "The ruminants show a considerably lower phosphoric acid content than the carnivora or the horse, pig and rabbit. Perhaps in the ruminants there is an organic acid present with the phosphoric acid."

ANALYSES OF THE BLOOD OF VARIOUS SPECIES OF MAMMALS

Abderhalden (1898) Parts per 1000 of Blood

	Pig-blood		Rabbit-blood		Dog-blood I		Dog-blood II		Cat-blood		Goat-blood	
	Blood corpuscles 435.09	Serum 564 91	Blood corpuscles 372.1	Serum 627.9	Blood corpuscles 407.3	Serum 592.7	Blood corpuscles 442.8	Serum 557.2	Blood corpuscles 434.0	Serum 566.0	Blood corpuscles 347.2	Serum 652.8
Water	272.20	518.36	235.74	581.18	262.41	547.64	277.71	514.30	270.90	524.17	211.35	592.54
Solids	162.89	46.54	136 37	46.71	144 90	45.05	165.10	42.89	163.11	41 35	135.86	60.25
Haemoglobin	142.2	....	123 5	.....	133.4	.....	145.6	.....	143.2	.....	112.5	.....
Protein	8.35	38.26	4.55	33.63	4 04	35.64	2.36	34 05	11.62	33.16	18.76	50.96
Sugar	.....	0.684	.....	1.036	.... .	1.084	.....	0 735	.....	0 860	.....	0.822
Cholesterin	0.213	0.231	0.268	0.343	0.878	0 420	0.556	0 366	0 556	0 339	0.601	0.698
Lecithin	1.504	0.805	1.722	1.105	1.046	1.006	1.017	0.977	1.354	0 971	1.339	1.127
Fat	.....	1.104	.....	0.749	.....	0 622	.....	0.914	.....	0 446	.....	0.0407
Fatty acids	0.027	0.448	.....	0.507	0.036	0.723	.....	0.698	.....	0.282	.....	0.398
Phosphoric acid as nuclein (P_2O_5)	0.0455	0.0123	0.040	0.015	0.045	0.009	0.045	0 009	0.063	0.009	0.028	0.0117
Soda (Na_2O)	.....	2.401	....	2.789	1.149	2.526	1.265	2.392	1.174	2.512	0.755	2.824
Potash (K_2O)	2.157	0.152	1.946	0.162	0.118	0.133	0.114	0.144	0.112	0.148	0.236	0.160
Iron oxide (Fe_2O_3)	0.696	.....	0.615	.....	0.641	.....	0.706	.....	0.694	.....	0.547	.....
Lime (CaO)	.....	0.0689	.....	0.072	.....	0.066	.....	0 061	.....	0 062	.....	0.078
Magnesia (MgO)	0.0656	0.0233	0.029	0.028	0.029	0.023	0.029	0.025	0.035	0.024	0.014	0.026
Chlorine	0.642	2.048	0.460	2.438	0.551	2.384	0.603	2.305	0 455	2.360	0.514	2.409
Phosphoric acid (P_2O_5)	0.8956	0.1114	0.335	0.151	0.666	0.143	0.673	0.139	0.697	0.133	0.243	0.154
Inorganic phosphoric acid (P_2O_5)	0.7194	0.0296	0.645	0.040	0.529	0.047	0 538	0.045	0.515	0.040	0.097	0.045

ANALYSES OF THE BLOOD OF VARIOUS SPECIES OF MAMMALS (CONCLUDED)
Abderhalden (1898) Parts per 1000 of Blood

	Sheep-blood I		Sheep-blood II		Ox-blood (1)		Bull-blood		Horse-blood I (2)		Horse-blood II	
	Blood corpuscles 306.3	Serum 693.7	Blood corpuscles 319.2	Serum 680.8	Blood corpuscles 325.5	Serum 674.5	Blood corpuscles 334.3	Serum 665.7	Blood corpuscles 529.7	Serum 470.3	Blood corpuscles 397.7	Serum 602.3
Water	185.25	636.42	200.39	624.16	192.65	616.25	206.81	608.03	324.79	424.23	243.87	551.14
Solids	121.06	57.27	118.82	56.63	132.85	58.249	127.50	57.66	204.91	46.07	153.84	51.15
Haemoglobin	92.9	.....	102.8	....	103.10	....	106.4	.....	166.9	.....	125.8	.....
Protein	24.03	46.82	12.8	46.56	20.899	48.901	15.38	46.41	30.08	39.62	20.05	42.65
Sugar	.....	0.735	.....	0.708	.....	0.708	.....	0.679	.....	0.551	.....	0.897
Cholesterin	0.723	0.609	1.147	0.891	1.100	0.835	0.610	0.599	0.266	0.140	0.263	0.313
Lecithin	1.035	1.185	1.329	1.088	1.220	1.129	0.953	1.244	2.105	0.8089	1.931	1.051
Fat	.....	0.937	.....	0.859	....	0.625	.....	2.357	.....	0.6113	.....	0.502
Fatty acids	.....	0.492	.....	0.4908		Not det.	.....	0.494		Not det.	0.024	0.363
Phosphoric acid as nuclein (P_2O_5)	0.0212	0.0073	0.0235	0.0109	0.0178	0.0089	0.0194	0.0089	0.0506	0.0094	0.050	0.009
Soda (Na_2O)	0.654	2.984	0.760	2.917	0.7266	2.9084	0.839	2.873	.....	2.0853	.....	2.624
Potash (K_2O)	0.228	0.177	0.236	0.172	0.2351	0.1719	0.233	0.174	2.6143	0.1237	1.323	0.152
Iron oxide (Fe_2O_3)	0.492	.....	0.545	.....	0.544	.....	0.562	.....	0.828	.....	0.592	.....
Lime (CaO)	.....	0.0811	.....	0.089	.....	0.0805	.....	0.073	.....	0.0523	.....	0.066
Magnesia (MgO)	0.005	0.028	0.006	0.027	0.0056	0.0300	0.009	0.027	0.0429	0.0211	0.039	0.027
Chlorine	0.506	2.574	0.575	2.516	0.5901	2.4889	0.628	2.453	1.0327	1.7523	0.183	2.201
Phosphoric acid (P_2O_5)	0.252	0.160	0.228	0.163	0.2392	0.1646	0.236	0.156	1.0072	0.1128	0.981	0.145
Inorganic phosphoric acid (P_2O_5)	0.1394	0.0506	0.088	0.057	0.1140	0.0571	0.133	0.041	0.7724	0.0336	0.762	0.045

(1) The items on ox-blood were taken from Abderhalden (1897), with alterations of the haemoglobin and protein figures made by the help of a note in Abderhalden (1898) p. 105.

(2) The items on the blood of horse I were taken from Abderhalden (1897).

Weiske (1886) analyzed the blood of lambs in connection with a study of the effects of ingestion of acids. From this work the following data are quoted.

INORGANIC ELEMENTS OF LAMB'S BLOOD
Weiske (1886) Percent, Dry Basis

Animal	P	N	K_2O	Na_2O	CaO	MgO	Feed, 6 months
Lamb I	0.150	15.255	0.415	2.220	0.066	0.029	Normal hay, barley
Lamb II	0.150	14.960	0.430	2.445	0.074	Trace	Hay treated with dilute H_2SO_4, barley
Lamb III	0.130	15.090	0.305	0.395	0.065	Trace	Killed at beginning of the experiment

For comparison with the data on blood of mammalia we quote the following figures for constituents of the blood of birds, from the work of Weiske.

DETERMINATIONS ON THE BLOOD OF BIRDS
Weiske (1889) Percent, Dry Basis

Bird	Mineral matter	N	CaO	MgO	P_2O_5
Fowl	5.99	14.84	0.12	0.08	1.69
Fowl	6.14	15.19	0.08	0.06	1.71
Fowl	5.57	15.22	0.06	0.06	1.82
Fowl	5.52	15.37	0.07	0.07	1.55
Fowl	5.85	15.11	0.10	0.07	1.79
Goose	5.27	15.98	0.04	0.09	1.77

Bergell (1898b) gives the following values of the phosphorus content of the blood ash of cattle: Blood of calf, 8.36, 6.73, 7.83 percent P_2O_5; of cow, 6.21 percent; of ox, 4.17, 5.06, 4.64, 5.66 percent. He thinks there is a significance in the ratio of serum phosphorus to erythrocyte phosphorus.

Bürger and Beumer (1913b) found lecithin in the blood cells of man and sheep in minute amounts only. The phosphatids consist chiefly of sphingomyelin, with some cephalin, an ether-soluble diaminomonophosphatid, and a water-soluble phosphatid.

PHOSPHORUS COMPOUNDS IN MILK

GENERAL COMPOSITION

It is the idea of Duclaux (1884a, 1884b, 1884c, 1893, 1894) that in milk both casein and calcium phosphate exist partly in suspension and partly in solution, the casein being, in fact, an equilibrium

Note: For a general discussion of the constituents, properties and changes of composition of milk the reader is referred to the review and summary of literature by Raudnitz (1903); also to Basch (1903) and Kastle and Roberts (1909).

of the three conditions solid, colloidal and dissolved. The phosphates in suspension are thought to be those of calcium, of magnesium and of iron or aluminum, the calcium phosphate in suspension being about twice the amount of that in solution.

Vaudin (1894a, 1894b, 1895, 1897b) finds alkali citrates in milk, which, aided by the presence of lactose, he considers essential for holding the calcium phosphate in solution.

Richmond (1901) looked upon casein as being a compound containing sodium, calcium and phosphorus united in the milk with $Ca_3(PO_4)_2$, the salts of the milk including also both mono- and di-basic phosphates. Richmond considers that of the 0.75 percent of ash in milk 0.27 percent is salts combined with casein, the remaining 0.48 percent being salts in solution in the milk plasma.

Söldner (1888) thought that the calcium united with casein is not a phosphate but the oxide only.

Barillé (1909a, 1909b), from microscopical and chemical examinations of milk, has put forth the idea that in it there are crystallizable compounds of the phosphates with carbonic acid which he calls "carbonophosphates," and which he considers beneficial for the assimilation of milk. Pasteurization, he states, precipitates and decomposes these carbonophosphates almost completely and hence is injurious. Sterilization with ultraviolet rays leaves the carbonophosphates intact, and is recommended. The data may be of interest.

CARBONOPHOSPHATES IN MILK AS AFFECTED BY STERILIZATION
Barillé (1909)—Grams

Milk analyzed	Sample No.	Phosphoric acid per liter, as P_2O_5			Carbonic acid per liter	
		Insoluble phosphates	Soluble phosphates	Carbono-phosphates	In free state and as carbonophosphates	As carbonates and dissociated carbonates
From Department at Seine-et-Marne	1	0.812	0.677	0.214	0.052	0.136
Commercial pasteurized milk sold in Paris	2	0.728	0.519	0.045	0.046	0.076
	3	0.767	0.711	0.011	0.043	0.072
	4	0.750	0.640	0.050	0.064	0.077
From dairy at Paris						
Fresh milk	5	0.521	0.540	0.372	0.078	0.140
Same pasteurized by us	5+	0.690	0.630	0.079	0.068	0.065
From dairy near Paris						
Drawn in our presence	6	0.666	0.530	0.372	0.132	0.173
Same pasteurized by us	6+	0.882	0.598	none	0.075	0.042
From dairy in Paris						
Fresh milk	7	0.660	0.350	0.210	0.091	0.148
Same submitted to ultraviolet rays	7+	0.710	0.370	0.190	0.080	0.107

Aside from inorganic phosphates and casein, in whatever combinations they may be present, there are other phosphorus compounds reported; a phosphatid, usually considered to be a lecithin, a nucleon similar to the phosphocarnic acid of muscle, and perhaps another phosphorized protein, the opalisin of Wróblewski (1894a, 1894b, 1898). He found opalisin present in abundance in human milk, in less quantity in mare's milk, and in very small amount in cow's milk.

The relative amounts of the constituents in milk are not constant, as is shown by the data we submit, and the milks of different species of mammalia differ. Naturally, a part, but not all, of the variations appearing in the tables are due to the use of different methods of determination. Schmidt-Mülheim (1883) compares the first and last portions drawn at milking. The last is always considerably richer in fat, but the fat-free serum does not vary much in composition.

The table of Ellenberger, Seeliger and Klimmer (1902) comparing the composition of the milk of woman, cow and ass will serve to show the general composition of milk, and some of the variations with species. Ellenberger's special study was on the milk of the ass. (See also Ellenberger, 1899, 1902.)

COMPOSITION OF ASS'S, WOMAN'S AND COW'S MILK
Ellenberger, Seeliger and Klimmer (1902)—Percent

	Ass's milk	Woman's milk	Cow's milk
Water	91.23	86.4	88.0
Dry matter	8.77	13.6	12.0
Protein	1.50	1.6	3.3
Casein	0.94	1.0	3.0
Albumin and globulin	0.53	0.5	0.3
Nucleon	0.1	0.12	0.06
Fat	1.15	4.8	3.5
Lecithin	0.02	0.06	0.05
Milk sugar	6 0	6.6	4 5
Salts	0.4	0.25	0.75

We quote below the averages of Katayama's (1908) extensive analyses of the milk of different pure breeds of cattle, and of the milk of unimproved native cattle from different countries. (The averaging has been done in the main by the compilers).

AVERAGE COMPOSITION OF MILK OF VARIOUS BREEDS OF CATTLE
Katayama (1908)—Percent

Breed	Number of samples	Dry substance	Fat	Nitrogen	Ash	Lime CaO	Phosphoric acid P_2O_5
Silesian red	3	13.39	4.63	0.580	0.705	0.152	0.216
Red-brown East Friesian	2	14.14	5.65	0.677	0.842	0.193	0.222
Scheinfelder ...	3	13.03	4 57	0.519	0.703	0.152	0.212
Voigtländer	3	12.39	4 19	0.543	0.778	0.162.	0.209
Simmenthal	3	13.94	4.66	0.625	0.781	0.196	0.238
Black-spotted East Friesian	3	12.03	3.22	0.605	0.784	0.193	0.247
Holland	3	12.86	4.32	0 545	0.738	0.166	0.236
Wilstermarscher	3	12.37	3.87	0 524	0.699	0.155	0.200
Swiss ,,	3	12.45	3.98	0.574	0.739	0.164	0.219
East Prussian Holland	6	11.12	3.16	0.449	0.713	0.154	0.188
Average of these improved breeds ..		12 55	4 08	0.547	0 742	0.167	0.216
Minimum		10.76	2.02	0.429	0.666	0.143	0.180
Maximum		14 95	6.36	0 682	0 863	0.227	0.273
Roumania	3	12.28	3.36	0.510	0.747	0.185	0.227
Ceylon	2	13.23	4.94	0.489	0.654	0.170	0.200
Korea	2	10.44	0.75	0.516	0.732	0.200	0.280
Dutch East Africa	6	12.40	4.08	0.680	0.708	0.176	0.225
Buffalo	1	9.69	4.37	0.336	0.467	0.150	0.153
Average of native breeds		12.04	3.60	0.567	0.695	0.178	0.225
Minimum		9.69	0.70	0.336	0.467	0.150	0.153
Maximum		13.60	5.89	0.649	0.795	0.204	0.296

DISTRIBUTION OF PHOSPHORUS IN MILK

As to the distribution of phosphorus among the constituents of milk we do not find close agreement in the evidence.

Raudnitz (1903) gives the following figures for phosphorus in various conditions, which must be looked upon as approximations. They differ considerably from other estimations which we quote.

PARTITION OF PHOSPHORUS OF MILK—(Raudnitz, 1903)

Species	Total P_2O_5 Percent	Casein P_2O_5		Lecithin P_2O_5 Percent	Preformed phosphoric acid		Authors mentioned
		Percent	Percent of total		Percent	Percent of total	
Cow.....	0.24	0.0581	about 21	0.005	0.18	about 79	.....
Woman.....	0.047	0.012	25	0.006	0.034	72	Baginsky
Ass.....	0.135	0.0117	8.2	0.005	rest	nearly 90	Dresden observers

Schlossmann (1905b) compared different milks, and the following values show a contrast between human and bovine milk in the amount of phosphorus present in inorganic form.

PARTITION OF PHOSPHORUS IN MILK—(Schlossmann, 1905b)

Species	Total P_2O_5 Gm. per liter	Casein P_2O_5		Lecithin P_2O_5		Nucleon P_2O_5		Rest. as inorganic
		Gm. per liter	Percent of total	Gm. per liter	Percent of total	Gm. per liter	Percent of total	Percent of total
Cow	1.65	0 58	35	0.091	5.5	0.09	5.5	54
Woman	0.455	0.16	35	0.16	35	0.153	33	0

Marre (1911) finds nearly all of the lecithin of cow's milk in buttermilk. He states that pasteurization of milk decomposes the lecithin.

Forbes, Beegle and Mensching (1913) found 56 percent of the phosphorus of skimmed cow's milk to be inorganic.

The partition of phosphorus as given by Gilbert and Posternak (1903, 1905) is as follows:

GRAMS P_2O_5 PER LITER OF MILK

Species	Total	In casein	In lecithin	In nucleon	Total organic
Cow	1.81	0.580	0.091	0.087	0.758
Woman	0.43–0.47	0.132	0.153	0.171	0.456

Stoklasa (1897) gives the average lecithin P_2O_5 of cow's milk as 0.091 gm. per liter, or 5 percent of the total, and that of woman's milk 0.153 gm. per liter, or 35 percent of the total, which agrees with Schlossmann. Jensen's (1904, 1905a, 1905b, 1905-6) details, reported from 15 milk analyses, distinguishing between the phosphorus of casein and that of insoluble or soluble salts, make the casein phosphorus about 25 percent of the total in cow's milk.

Values reported by Paton, Dunlop and Aitchison (1899-1900) indicate that in goat's milk the phosphorus of casein and lecithin is about 29 percent of the total; that of nucleon is about 16 percent, and the inorganic about 55 percent of the total.

Sikes (1906) made about three hundred estimations of phosphorus, and a somewhat smaller number of determinations of calcium, on human milk. The following are his conclusions:

Phosphorus: 1. The average amount of P_2O_5 in human milk during the first fortnight after the commencement of lactation is 0.0297 percent, the variations being between 0.0140 and 0.0522 percent.

2. The percentage of the non-proteid P_2O_5 averages 0.0169, and of the proteid P_2O_5 0.0124, for the total number of cases. For primipara and for multipara the numbers are 0.0160 and 0.0129, and 0.0183 and 0.0116, respectively.

3. The ratio of the proteid P_2O_5 to the total P_2O_5 averages 42.3 percent, but it varies between 14.7 and 77 percent. In primipara the average is 44.6 and in multipara 38.8 percent.

4. The chart for primipara shows that the total amount of P_2O_5 increases up to the ninth day, while that for multipara shows a maximum a little earlier. After this in both the P_2O_5 falls to a lower level.

5. The variations mentioned are chiefly due to the non-proteid P_2O_5.

6. The proteid P_2O_5 does not vary much on successive days. This uniformity is rather more noticeable in multipara than in primipara.

7. If one assumes that the average amount of proteid in human milk is 2 percent, the numbers mentioned will give the average amount of P_2O_5 in it as 0.62 percent. For primipara the number will be 0.64 and for multipara 0.58 percent.

Calcium. 1. The average amount of calcium in human milk in the first fortnight after delivery is 0.0301 percent.

2. In primipara the average is slightly lower than in multipara.

3. The major part of the calcium is combined with the proteid. The ratio of the proteid calcium to the total calcium is, on the average, 84 to 100.

4. The variations of the calcium from the average stated are small.

5. The curve giving the percentages on successive days after delivery is more uniform than the similar curve of the percentages of P_2O_5 in the same samples.

6. When both the calcium and the proteid were estimated on the same samples, the calcium was found to average 1.06 percent of the total proteid.

Njegovan (1913) investigated the lecithin content of milk by a carefully considered method, and concluded that the existence of lecithin in milk is doubtful.

MINERAL CONSTITUENTS OF MILK

We have brought together from various sources a number of individual or average determinations of the mineral constituents of the milks of different species, grouping them as to species. No attempt was made to consider the methods of analysis.

MINERAL CONSTITUENTS OF THE MILK OF DIFFERENT SPECIES AS REPORTED BY VARIOUS AUTHORS—Percents, or Grams per 100 C. C.

Species	Author	Reference date	Ash	K_2O	Na_2O	CaO	MgO	Fe_2O_3	P_2O_5	Cl	Notes
Human...	Bunge	1874	0.2203	0.0741	0.0244	0.0335	0.0065	0.0005	0.0471	0.0441	Mean of 2 computed by compilers.
Human. ..	de Lange	1897, 1900	0.32	0.0642	0.0953	0.0415	0.0092	0.0008	0.0577	0.0686	
Human ...	Backhaus and Cronheim	1900		(30.54)	(13.90)	(16.44)	(2.65)	(1.19)	(13.27)	(19.70)	SO_3=5.11 percent. Percent of ash. Mean of 2 computed by compilers.
Human....	Söldner (with Camerer)	1902	0.3098	0.1008	0.0448	0.0376	0.0054	0.0002	0.0321	0.0717	Also Camerer and Soldner, 1900 and 1902, 1903. Early in lactation period.
Human....	Soldner (with Camerer)	1902	0.1987	0.0634	0.0176	0.0381	0.0052	0.0001	0.0288	0.0342	Later in lactation period.
Human...	Soldner (with Camerer)	1902	0.2728	0.0884	0.0357	0.0378	0.0053	0.0002	0.0310	0.0591	Mean of all analyses made.
Human....	Tobler and Noll	1910	0.1596	0.0480	0.0309	0.0334			0.0294		One case.
Human....	Marre	1911a		0.0939 [2]	0.0741 [2]	0.0364 [2]	0.0066 [2]	0.001	0.031 [3]	0.046	Milk of 20th day. [2]Computed from elements by compilers.
Human....	Marre	1911a		0.0782 [2]	0.0620 [2]	0.0308 [2]	0.0050 [2]	0.001	0.024 [3]	0.042	Milk of 10th month. [3]Phosphoric acid.
Ass.....	Ellenberger	1902	0.3-0.5	0.084	0.033	0.106	0.013	0.001	0.135	0.031	
Mare.....	Bunge	1874	0.418	0.1045	0.0139	0.1236	0.0125	0.0015	0.1309	0.0308	
Buffalo....	Schrodt	1889	0.744	0.1053	0.0455	0.2512	0.0241	0.0013	0.2532	0.0550	Computed by compilers from percent of ash.
Cow.....	Bunge	1874	0.836	0.1766	0.1110	0.1599	0.0210	0.00035	0.1974	0.1697	In Bunge's report "ash" is sum of oxides minus oxide equivalent to chlorine.
Cow.....	Schrodt and Hansen	1885	(103.20)	(25.41)	(10.94)	(21.45)	(2.54)	(0.11)	(24.11)	(14.53)	Percent of ash. Compilers averaged 7 analyses for different seasons of year.
Cow.....	Trunz	1903	{ 0.5780- { 0.9990	0.1289- 0.2120	0.0211- 0.1651	0.1524- 0.2841	0.0165- 0.2266	0.0009- 0.0045	0.1821- 0.3284	0.0630- 0.2321	Gm. per 100 cc. Mean of 64 throughout lactation of 2 cows.
Cow.....	Jensen	1904		0.1833	0.0436	0.1831	0.0173	.....	0.1983	0.1014	Mean of 15 computed by compilers. Different proportions, hay and beets.
Cow.....	Babcock	....	0.7	0.175	0.070	0.140	0.017	0.001	0.170	0.100	SO_3=0.027. Quoted by Leach, Food Inspection and Analysis.
Cow.....	Sherman	1911		0.171	0.068	0.168	0.019	0.00034 [1]	0.215	0.12	Sherman's values are from compilations. [1]Computed from Fe by compilers.
Sheep.....	Weiske and Kennepohl	1881	(101.74)	(30.16)	(5.79)	(34.76)	(2.67)		(19.50)	(7.79)	SO_3=1.07. Percents of ash.
Sheep.....	Proscher	1898		0.1174	0.1078	0.2717	0.0500	0.0037	0.4123	0.1344	
Sheep	Abderhalden	1899d	0.8406	0.0967	0.0864	0.2453	0.0148	0.0041	0.2928	0.1297	
Goat.....	Proscher	1898		0.2345	0.0523	0.2104	0.0363	0.0015	0.3215	0.2038	
Goat.....	Abderhalden	1899d	0.7713	0.1302	0 0617	0.1974	0.0154	0.0036	0.2840	0.1019	
Guinea pig.	Abderhalden	1899d	0.7779	0.0754	0.0700	0.2417	0.0241	0.0013	0.2880	0.0999	
Rabbit. ...	Abderhalden	1899d		0.2516	0.1980	0.8914	0.0552	0.0020	0.9966	0.1355	
Pig.....	Abderhalden	1899d	0.8338	0.0996	0.0799	0.2577	0.0164	0.0042	0.3172	0.0796	Mean of 3 computed by compilers.
Pig.....	Scheven	?	1.09	0.0678	0.0734	0.4275	0.0193	0.0095	0.4056	0.1016	{ Quoted by Burr (1907). Computed by compilers
Pig.....	Ramoot	?	1.09	0.0845	0.0889	0.4079	0.0234	.....	0.3497	0.1206	{ from percent of ash.
Dog.....	Bunge	1874	1.3058	0.1548	0.0751	0.4406	0.0206	0.0016	0.4805	0.1715	Mean of 2 computed by compilers.
Dog.....	Bunge	1889	1.1355	0.1701	0.1000	0.3093	0.0175	0.0014	0.3886	0.1919	
Dog.....	Abderhalden	1899d	1.3282	0.1382	0.0779	0.4545	0.0195	0.0020	0.5078	0.1656	

On the basis of analyses of milk and of its serum and its ash, Söldner (1888) gives the following as the forms and amounts of mineral constituents present in one liter of milk: NaCl 0.962, KCl 0.830, KH_2PO_4 1.156, K_2HPO_4 0.835, potassium citrate 0.495, dimagnesium phosphate 0.336, magnesium citrate 0.367, dicalcium phosphate 0.671, tricalcium phosphate 0.806, calcium citrate 2.133, calcium oxide of casein 0.465. He considered only calcium oxide to be united with the casein.

Vaudin (1897a) made determinations of total mineral matter, and of earth phosphates in milk of different breeds of cows, from different countries,with different feeds, and when different quantities of milk were being produced, with the conclusion that none of these factors has much influence on the quantity of ash or on its earth phosphate content. The total mineral matter found ranges from 7.05 to 7.83 gms. per liter in all the normal cases except two (two are 8.10 and 8.66 respectively) and the earth phosphates from 3.30 to 4.10 in all cases.

Friedenthal (1911) has computed the number of ions of the inorganic constituents present in the milk of several species, especially the number supplied by diluted cow's milk and by woman's milk. These computations are based on analyses by Schloss. A table gives the anions and cations (K,Na,Mg,Ca,Cl,PO_4 and the rest as citric acid) per liter of the milk of each species. The PO_4 values stated are : human milk 2.73×10^{-3}, cow's milk 13.46×10^{-3}, sow's milk 16.8×10^{-3}, dog's milk 35.76×10^{-3}, rabbit's milk 70.18×10^{-3}, ass's milk 15.7×10^{-3}. The relation of these numbers to one another indicates the relative amounts of inorganic phosphate in the milks, showing human milk to have a low value, and that of the dog and rabbit very high values in this respect.

Schloss (1911) reports the following analyses of woman's milk from 24-hour samples, the first being a mean of analyses of milk from 8 women, the second and third representing the mixed milk of 16 and 15 women respectively.

ANALYSES OF WOMAN'S MILK—Parts per Liter

	Mean of 8 analyses	Mixed milk I	Mixed milk II
Fat	37.88	40.225	35.87
Nitrogen	1.847	1.904	1.897
Total ash	1.839	1.913	1.838
CaO	0.3758	0.3856	0.380
MgO	0.0857	0.0761	0.0725
Na_2O	0.1886	0.1623	0.1958
K_2O	0.5291	0.5292	0.5360
P_2O_5	0.4046	0.4469	0.3829

CASEIN CONTENT OF MILK

For each of the organic phosphorus compounds, also, we have collected a table from the individual determinations.

CASEIN CONTENT OF THE MILK OF DIFFERENT SPECIES OF MAMMALS—Percent

Author	Reference, date	Species									Notes
		Cow	Human	Ass	Sheep	Goat	Pig	Dog	Others		
									Kinds	Casein	
Blyth	1879	3.98									
Voelcker	1880a, 1880b				5.24 [1], 17.37 [2]	3.93 [3]					[1]Mean of 8. [2]Colostrum. [3]Mean of 3.
Meigs, A. V.	1882		0.7-1.0								
Meigs, A. V.	1883		1.046								
Schmidt-Mülheim	1883	2.25									Gm. per 100cc. Mean of 8. Some first and some last drawn.
Strohmer	1888								Buffalo	3.99	
D'Hont	1890	3.50									
Doremus	1890								Elephant	2.95	Mean of 2.
Pappel and Richmond	1890								Gamoose	3.26	
Hempel (Lehmann's work)	1894	3.0	1.2								
Schlossmann	1897			0.981							Including traces of globulin.
Seeliger	?			0.832							Mean of 2. Quoted by Schlossmann.
Munk	?			0.7							Quoted by Schlossmann.
Abderhalden	1899a							4.62	Cat	3.71	
Abderhalden	1899a								Rabbit	8.17	
Abderhalden	1899d				4.08	2.91	3.58	4.82	Guinea pig	4.70	Average up to time of doubling weight of young.
Abderhalden	1899d				4.07	2.56	3.17	4.42	Guinea pig	4.21	Average after doubling weight of young.
Richmond	1901	3.33									With salts in combination.
Edlefsen	1901		1.810-0.310								From 3rd to 116th day of lactation.
Ellenberger, Seeliger and Klimmer	1902	3.0	1.0	0.94							Perhaps not all the work of these authors.
Bordas and de Raczkowski	1902b	2.88									
Trunz	1903	2.599									Mean of 60.
Jensen	1904, 1905b	2.64									Different proportions of hay and beets.
Von Szontagh	1905	2.48	0.66	0.84		2.22			Buffalo	3.59	Gm. per 100cc.
Von Szontagh	1905								Mare	0.92	Gm. per 100cc.
Hart	1907	2.69									Computed from 26.
Ostertag and Zuntz	1908						7.45				Average of many analyses.
VanSlyke and Bosworth	1909	3.08									Mean of 15; 2 methods; computed by compilers.
Leach—extremes	1909	1.79-6.29	0.18-1.96		3.59-5.69	2.44-3.94					Compiled from König's tables.
Leach—mean	1909	3.02	1.03	0.67	4.97	3.20			Mare	1.24	Compiled from König's tables.
Hart	1909	2.82									Computed from 40 by compilers.
Engel and Frehn	1910		0.49								Mean of 35; computed by compilers.
Martin	1911				6.67						Gm. per 100 cc. Mean of 6 monthly averages.

Rogers (1909) gives the casein content of buttermilk as 2.4, of kefir 2.56-2.59 and of kumiss 0.77-0.85 percent.

Engel and Frehn (1910), computing the casein content of human milk from the nitrogen loss of the milk on precipitation with acetic acid, report the examination of 31 samples from several wet nurses, at different times in the lactation period, and of four samples of mixed milk, from which they conclude: "The relative casein value of human milk undergoes wide variations, even with the same individual, for which no laws could be recognized. The factors which have empirically been taken to be of great influence for the composition of human milk, like the time of lactation, individuality, the phase of the emptying of the breast, or the length of intervals between nursing, play no recognizable part in determining the casein content."

PHOSPHATID CONTENT OF MILK

The content of phosphatid in milk varies with the time of lactation, and is reduced by heating, as well as by skimming. Fetzer (1910) has noticed that the milk from animals suffering from mastitis contains less lecithin than that from healthy animals. It was further noted that where a diminution in the lecithin content took place there was a corresponding decrease in the fat content.

Very few of the studies have distinguished lecithin in milk from other phosphatids possibly present. W. Koch (1906) thought he identified both lecithin and cephalin in milk.

Wrampelmeyer (1892) reports that 100 gm. of butter contains 0.0451 gm. P_2O_5, indicating 0.017 percent lecithin.

PHOSPHATID OF MILK OF DIFFERENT SPECIES AS REPORTED BY VARIOUS AUTHORS—Reported as Percent Lecithin

Author	Date	Species							Notes
		Cow	Human	Ass	Dog	Sheep	Goat	Mare	
Stoklasa	1897	0.090-0.113	0.170-0.186						Gm. per 100 cc. milk
Burow	1900	0.054	0.058		0.17				
Ellenberger	1902	0.05	0.06	0.024					
Nerking and Haensel	1908	0.0364-0.1163	0.0240-0.0799	0.0058-0.0393		0.0509-0.1672	0.0349-0.0753	0.0073-0.0174	Extremes
Glikin	1909b	0.0765	0.1329						
"	"	0.0629 (17)	0.0499 (10)	0.0165 (6)		0.0833 (4)	0.0488 (11)	0.0109 (8)	Average and no. of analyses
Kida	1909	0.0449							Gm. per 100 cc. milk Mean of 4

NUCLEON CONTENT OF MILK

The nucleon content of the milk of woman, the goat and the ass are shown by the following figures to be somewhat nearly the same, while cow's milk seems to contain only half as much of this constituent.

NUCLEON CONTENT OF MILK OF DIFFERENT SPECIES AS REPORTED BY VARIOUS AUTHORS—Computed as Carnic Acid, Percent or Grams per 100 c. c. Milk

Author	Date	Species				Notes
		Cow	Human	Ass	Goat	
Siegfried	1896	0.0583				Gm. per 100 cc. Mean of 2 computed by compilers.
Blumenthal	1896	0.0502				Gm. per 100 cc. Decreases on standing.
Wittmaack	1897	0.0566	0.124		0.110	5 cows; 8 women; 4 goats.
Schlossmann	1897			0.120		
Ellenberger, Seeliger and Klimmer	1902			0.1		
Valenti	1905, 1908		0.1315			Average for year. Mean of 3 computed by the compilers.

Blumenthal (1896) found that the 0.5021 gm. carnic acid (measure of phosphocarnic acid) in a liter of cow's milk decreased to 0.2430 gm. while the milk stood at room temperature for eight days. This is taken as indicating that phosphocarnic acid is a source of the decomposition products of milk.

SOME COMPARISONS OF WHOLE MILK, SKIMMED MILK AND CREAM

A considerable part of the lecithin of milk and a smaller proportion of the casein are removed with the cream; hence skimmed milk is richer in casein and much poorer in lecithin than whole milk. Bordas and de Raczkowski (1902b), however, claim that the lecithin is not wholly removed in the cream, while Glikin (1909b) does not agree with them, and says that if the cream is completely separated by centrifuging the lecithin is also completely removed. Following are Bordas and deRaczkowski's analyses of milk, 3.200 liters of which gave 2.800 liters of skimmed milk and 0.370 liters of cream.

PHOSPHORUS COMPOUNDS IN WHOLE MILK, SKIMMED MILK AND CREAM—Grams per 100

	Whole milk	Skimmed milk	Cream
Casein	2.88	3.24	1.15
Total phosphoric acid	0.176	0.184	0.096
Organic phosphoric acid	0.0044	0.0013	0.0252
As glycerophosphoric acid	0.0124	0.0037	0.0691
As lecithin	0.058	0.018	0.334

The figures below are from d'Hont (1890), who obtained 12 liters of skimmed milk and 3.5 liters of cream from 15.5 liters of whole milk.

ANALYSES OF WHOLE MILK, SKIMMED MILK AND CREAM

Percent

	Whole milk	Skimmed milk	Cream
Butter	5.05	0.025	21.95
Lactose	4.70	5.05	3.32
Casein	3.50	3.62	3.02*
Ash	0.79	0.788	0.585
Lime	0.22	0.214	0.155
Phosphoric acid	0.226	0.22	0.17

* From Kjeldahl nitrogen determination.

Dornic and Daire (1910) report that buttermilk contains more lecithin than whole cow's milk, and more even than woman's milk.

CHANGES OF PHOSPHORUS COMPOUNDS AS A RESULT OF HEATING OR STANDING

Baginsky (1883) found that heating milk to 120°, and dehydrating as in Scherff's method of preservation, did not decrease the ratio of phosphorus in casein to phosphorus in the whey.

Bordas and de Raczkowski (1903) noted that milk heated to various temperatures over the free flame, on the water bath, or in the autoclave loses through decomposition a certain amount of its lecithin. Diffloth (1904) also studied the effects of heating on milk. He found that a like effect is produced by simply allowing the milk to stand. Comparisons were made of the phosphorus changes due to standing and to heating as in sterilization or pasteurization. Total phosphorus was determined on the solids taken up by acetic acid, soluble inorganic phosphorus on the clear liquid left after complete coagulation, soluble organic on the same (this is interpreted as lecithin), and the insoluble phosphorus by difference. According to these figures, and the author's interpretation of them, lecithin decomposition takes place even when the milk stands at ordinary temperature, but heating causes a much greater change. The duration of heating seems to have a greater influence than the degree of heat; but with the same length of time of heating the diminution of assimilable phosphates (formation of insoluble phosphates and decomposition of lecithin) increases as the temperature increases. (See table on next page.)

Kida (1909) reports the following percentages of reduction in the lecithin content of cow's milk as a result of heating for thirty minutes at different temperatures: 80°, 7.52 percent; 80°, 11.39 percent; 95°, 25.27 percent; 100°, 21.22 percent.

Grosser (1913) finds that boiling milk 5-30 minutes does not alter the freezing point or the phosphorus content of that portion of the milk which passes through a Bechold filter—colloids are held back.

PHOSPHORUS PARTITION IN COW'S MILK AS AFFECTED BY STANDING AT 15° C. AND AT HIGHER TEMPERATURES
Diffloth (1904)—Grams P_2O_5 per Liter of Milk

Time of standing	Temperature	Total phosphorus	Soluble inorganic	Soluble organic	Insoluble	Increase in insoluble	Decrease in lecithin
2 hrs.	15°C	4.58	1.92	2.12	0.54	...	...
24 hrs.		4.58	1.92	2.08	0.58	0.04	0.04
48 hrs.		4.58	1.96	2.01	0.61	0.07	0.11
30 min.	60°	4.58	1.85	1.90	0.83	0.29	0.22
60 min.	60°	4.58	1.81	1.60	1.17	0.63	0.52
30 min.	95°	4.58	1.82	1.50	1.26	0.72	0.62
60 min.	95°	4.58	1.79	1.47	1.32	0.78	0.65
30 min.	110°	4.58	1.75	1.38	1.45	0.91	0.74

CHANGES IN MILK WITH PROGRESS OF LACTATION

Cow's Milk. Houdet (1894) made a chemical study of colostrum of the cow. From his conclusions we quote the following: "The composition of colostrum remains about the same from the time the liquid appears until after the birth of the young. In the days following the birth marked changes occur at once." Among the changes noted is this, "The calcium phosphate and other salts, abundant at first in both soluble and insoluble condition, diminish gradually until about the fourth or fifth day, when they show about the same content as in normal milk."

In the main, the observations of Trunz (1903) correspond with this last statement of Houdet, though perhaps there was longer time in getting back to normal, (6-7 days for one cow). Trunz made complete analyses of the milk of two cows at frequent intervals (30 samples for each) throughout lactation. We have computed a few summary statements from the phosphorus data. For further detail the original article should be consulted.

PHOSPHORUS OF MILK AS AFFECTED BY PERIOD OF LACTATION
Trunz (1903)—Grams per 1000

Cow No.	Day of highest phosphorus content	First 4 days				Average of later values		
		Total P_2O_5		P_2O_5 in salts		Number of samples	Total P_2O_5	P_2O_5 in salts
		Minimum	Maximum	Minimum	Maximum			
655	Day of calving	2.227	3.284	1.534	2.564	25	2.015	1.529
674	Day after calving	2.137	3.144	1.564	2.557	19	2.075	1.622

According to the statements of Kort (1899), based on a number of investigations, the content of cow's milk in mineral matter, particularly in phosphoric acid and calcium, decreases more or less regularly as the time of birth of the calf draws near, even in spite of decreased flow of milk; the colostrum is rich in ash; the percentage of phosphoric acid and calcium in the milk is lowest when lactation is at full height, though the absolute quantity is then the greatest.

Schrodt and Hansen (1885) determined the ash composition of the milk of the same cows (10) at seven dates between January and September, the times of calving having been October 15 to January 1. The cows were in stall from January to May, and in pasture from June to September. The phosphoric anhydride data, in percent of the ash, are as follows: January 1, 23.11; March 30, 23.11; May 20, 24.61; June 16, 22.41; July 26, 23.59; August 30, 26.51; and September 26, 25.41.

Bordas and de Raczkowski (1902a) report the following figures, and say that both the phosphoric acid and the lecithin constantly fall off in amount after the time of calving, animals of the same breed, and fed in the same way, showing the milk of the first month to be highest in lecithin.

PHOSPHORUS CONSTITUENTS IN MILK OF COWS AT DIFFERENT STAGES OF LACTATION (Bordas and de Raczkowski, 1902)—Percent

Breed	Jersey						Normandy
Date of calving	Cow with calf	July 4	July 1	June 12	May 13	Not with calf	
Casein content	3.86	3.17	2.90	2.89	3.04	2.80	2.61
Total phosphoric acid	0.218	0.204	0.200	0.164	0.168	0.148	0.156
Other organic phosphoric acid	0.0049	0.0068	0.0044	0.0033	0.0033	0.0041	0.0031
As glycerophosphoric acid	0.0139	0.0198	0.0124	0.0100	0.0100	0.0116	0.0093
As lecithin	0.0654	0.0909	0.0582	0.0472	0.0472	0.0545	0.0436

Note: The date of taking the samples is not given; samples probably taken all on the same date.

The general question of the influence of the stage of lactation on the composition and properties of milk has been studied by Eckles and Shaw (1913). They analyzed samples taken throughout the year from 11 cows of four breeds which were kept on a uniform ration of alfalfa and grain, and from 5 other Jersey cows not kept on uniform rations. The casein seldom went beyond the limits of 80 to 82 percent of the total protein, and averaged 81.4 percent. Both total protein and casein were abnormally high following

parturition, then declined continuously till the third or fourth week, when the minimum was reached. They then remained fairly constant until near the end of the lactation period, when they rose rapidly and reached the maximum at the end of the period.

Human Milk. Schlossmann (1905b) gives the following values for the total phosphorus in woman's milk at different times, indicating no characteristic change with duration of lactation.

Day of lactation	12	21	213	191 (right breast)	191 (left breast)	191 (right breast)	191 (left breast)
Grams per P_2O_5 per liter..	0.65	0.56	0.52	0.37	0.35	0.51	0.34

Engel and Frehn's opinion that the wide variations in casein content observed in human milk are not due to the stage of lactation has been mentioned above (see p. 162). Edlefsen (1901) gives a table of the gross analysis of human milk at different periods. Casein appears regularly to decrease with advance in period of lactation.

ANALYSES OF HUMAN MILK AT DIFFERENT PERIODS OF LACTATION
Edlefsen, (1901)—Percent

Day of lactation	Total protein	Casein	Albumin	Fat	Sugar
3	2.695	1.810	0 885	3.225	3.59
12	1.875	1.160	0.715	3.035	5.15
48	1.00	0 44	0 560	3.64	7.06
103	0.843	0.375	0.468	3.415	5.835
116	0.835	0.310	0.525	4.105	5.95

Valenti (1905, 1908) found that the content of nucleon in human milk is greatest during the first and second months of lactation, generally decreasing from the third to the sixth month, increasing again during the seventh month, and then remaining constant until the twelfth month.

RELATIONS OF THE COMPOSITION OF MILK TO THAT OF THE YOUNG

VonBunge (1874), in connection with studies of the alkalis of milk and other articles of diet and of the young organism, introduced the idea which became known as Bunge's law that the composition of the ash of milk (with the exception of the iron) corresponds closely with that of the ash of the total organism of sucklings. VonBunge (1886, 1889) and his pupils Abderhalden (1899b, 1899c) and Proescher continued to investigate the question, considering first whether the ash of blood and blood serum also have

the same composition, and whether there are characteristic differences between the species in this respect running parallel in the milk and the body of the young. Pagès (1894) criticized the supporters of Bunge's law on the ground that it was too sweeping, and that it was applied to all ash constituents, not distinguishing those which are essential for the growth of the bodies. We have not seen Pagès's thesis. A little later Proescher (1898) and Abderhalden (1899a, 1899d) compared the composition of the milk of each species in relation to the time required by the young of that species to double their live-weight. The numerical support for the idea of such a relation is best illustrated by the table below, taken from Abderhalden (1899d, p. 594). Protein, ash, lime and phosphoric acid in the milk of this series of animals all increase in the same order as does the rate at which the young double their weight.

RELATION OF THE COMPOSITION OF THE MILK OF DIFFERENT SPECIES TO THE TIME REQUIRED FOR THE YOUNG OF THE SAME SPECIES TO DOUBLE IN WEIGHT

Abderhalden (1899)

Species	Time required for the new-born animals to double the body weight	100 parts by weight of milk contain			
	Days	Protein	Ash	Lime	Phosphoric acid
Man	180	1.6	0.2	0.0328	0.0473
Horse	60	2.0	0.4	0.124	0.131
Cattle	47	3.5	0.7	0.160	0.197
Goat	22	3.67	0.7713	0.1974	0.2840
Sheep	15	4.88	0.8406	0.2453	0.2928
Swine	14	5.21	0.8071	0.2489	0.3078
Cat	9½	7.00	1.02	.....	.....
Dog	9	7.44	1.3282	0.4545	0.5078
Rabbit	6	10.38	2.4998	0.8914	0.9967

With regard to human milk, and the body of the human infant, investigation has yielded results which do not support the theory, or which at least show that the parallelism is less close here than for other animals. See the work of Cornelia deLange (1897, 1900), of Hugounenq (1899b, 1900), and of Camerer and Söldner (W. Camerer, Jun. 1900, 1902a; W. Camerer, Jun. and Söldner, 1900, 1903; Söldner, 1902).

Another suggestion has been made by Burow (1900) to the effect that there may be a significant relation between the lecithin content of the milk of different species and the brain weight of the suckling young of the same species. For cattle, dogs and men it was found to hold that the greater the relative brain weight, the higher is the lecithin content of the milk, reckoned in percent of the protein. "Here also nature has matched the needs of the sucklings with the composition of the milk."

COMPARISON OF THE RELATIVE LECITHIN CONTENT OF MILK AND THE RELATIVE BRAIN WEIGHT OF THE YOUNG OF DIFFERENT SPECIES—(Burow, 1900)

Species	Mean composition of milk				Brain weight: body weight
	Lecithin Percent	Protein Percent	Ash Percent	Lecithin: protein=X:100	
Cattle	0.054	3.84	0.69	X=1.40	1:370 (mean of 4, 7-8 wks. old.)
Dogs	0.17	8.05	1.00	2.11	1:30 (mean of 4, 5 days old.)
Men	0.058	1.90	0.24	3.05	1:7 (quoted from Vierordt.)

STUDIES OF THE PHOSPHORUS OF EGGS

General Composition and Phosphorus Content. All of the types of phosphorus compounds found in eggs, with the exception of nuclein, were noted by Gobley (1846, 1847) in his researches on hen's eggs and on the eggs of carp (1850a). The compounds are nuclein, phosphorized fat, nucleoalbumin and traces of inorganic phosphate.

Liebermann (1888a) made chemical examinations of different portions of the yolk and of the white. He also followed the special chemistry of the embryo through to the maturity of the chick. He found nuclein and lecithin in the germ; but no phosphorus in the ether extract of the yolk; he concluded, therefore, that the lecithin present is not free, but is in chemical combination, perhaps with vitellin, as previously suggested by Hoppe-Seyler. Extraction with water, or with dilute acid failed to reveal any phosphate directly recognizable without ashing.

According to Kaas (1906), the amount of phosphorus in the white is increased by remaining in contact with the yolk. T. B. Osborne and Campbell (1900c) report 0.122 percent phosphorus in the ovalbumin of egg white.

Carl Voit (1877a) gives the average phosphoric acid content of the white of one egg as 0.007043 gm., which would be 0.197 percent, and that of the yolk as 0.20386 gm., which would be 2.57 percent. Lebbin (1900, 1901) found an average of 0.22 percent P_2O_5 in the whites of hen's eggs and 1.43 percent in the yolks, or 0.636 percent in the whole edible part. Forbes, Beegle and Mensching (1913) found only traces of inorganic phosphorus in the edible portion of the hen's egg.

According to Hammarsten (1911, p. 600, 604) Poleck and Weber found 1000 parts of the ash of the white of the egg 276.6-284.5 parts potash, 235.6-329.3 soda, 17.4-29 lime, 17-31.7 magnesia, 4.4-5.5 iron oxide, 238.4-285.6 chlorine, 31.6-48.3 phosphoric acid (P_2O_5), 13.2-26.3 sulphuric acid, 2.8-20.4 silicic acid and 96.7-116

parts carbon dioxide. In 1000 parts of the ash of the yolk were found 51.2-65.7 parts soda, 80.5-89.3 potash, 122.1-132.8 lime, 20.7-21.1 magnesia, 11.90-14.5 iron oxide, 638.1-667.0 phosphoric acid, and 5.5-14.0 parts silicic acid.

Carpiaux (1908) gives the makeup of the ash of a fresh egg as being 17.37 percent K_2O, 22.87 percent Na_2O, 10.91 percent CaO, 1.14 percent MgO, 0.39 percent Fe_2O_3, 37.62 percent P_2O_5, 0.32 percent SO_3 and 8.98 percent Cl.

Malcolm (1902) has given us a comparison of the chemical composition of the yolks of eggs laid by different hens of the same breed, and on the same diet; also of the different eggs laid by the same hen on a constant diet. His tables are given in part below. The conclusions are: 1. The percentage of lecithin in egg-yolk varies considerably. 2. The percentages of protein, fat and phosphorus in the yolks of eggs from the same hen are in very close agreement, while there are very considerable differences in eggs from a number of hens, even where the breed is the same.

ANALYSES OF EGG-YOLKS—(Malcolm, 1902) Percent

	Egg No.	Fat	Nitrogen	P_2O_5	Ether extract		Chloroform extract	
					Percent	P_2O_5 content	Percent	P_2O_5 content
Unknown origin	1	27.786	3.004	1.489				
	2	29.453	2.620	.....				
Laid by hens all of one breed, and fed on maize and barley	3	28.501	2.648	1.356				
	4	28.662	2.674	1.527	28.662	0.1408	31.418	0.2085
	5	31.887	2.676	1.396				
	6	28.956	3.123	1.517	28.956	0.2120	31.423	0.2419
	7	29.114	2.877	1.511	29.114	0.1884	32.659	0.1930
	8	30.080	2.674	1.569	30.080	0.1838	33.100	0.2036
	9	.....	2.605	.....				
	10	30.124	2.822	1.471				
	11	29.565	2.846	1.654				
	12	.....	2.762	1.543				
Laid by one hen	13	31.043	2.575	1.392				
	14	31.575	2.552	1.425				
	15	30.431	2.607	1.441				
Lain by one hen	16	30.120	2.754	1.477				
	17	.....	2.797	.....				
	18	30.265	2.747	1.506				

THE NUCLEOALBUMINS OF EGGS

The nucleoalbumin of hen's eggs, ovovitellin, seems to be present in chemical combination with lecithin, and, as isolated and prepared, it usually contains lecithin. According to T. B. Osborne and Campbell (1900b), it is extracted as a mixture of several protein-lecithin compounds which may be called lecithin-nucleo-vitellins. Plimmer (1908) reports another protein containing less phosphorus than vitellin.

The corresponding compound from fish eggs, called ichthulin, was especially studied by Valenciennes and Frémy (1854) in their general consideration of the composition of salmon eggs; but G. Walter (1891) gave it a more particular study, as he obtained

it from the eggs of carp, and he decided that vitellin and ichthulin may be considered identical. Hammarsten (1905a) isolated a nucleoalbumin from the eggs of perch which yielded a much larger proportion of pseudonuclein, on pepsin digestion, than Walter had found from the ichthulin of carp eggs.

NUCLEIC ACID OF FISH EGGS

J. A. Mandel and Levene (1906b) obtained a nucleic acid from unfertilized fish eggs which in its chemical makeup resembled nucleic acids of plant origin more than those from animal substances generally. Helene Tschernorutzky (1912a) found indication of about 1.2 gm. nucleic acid in 100 gm. of dry, ripe, unfertilized herring eggs which had been extracted with alcohol and ether. The phosphorus content of the substances not removed by alcohol and ether was not all accounted for by this nucleic acid.

THE PHOSPHATIDS OF EGGS

A large part of the study of phosphatids, under the name of lecithin, has been made on that obtained from eggs. (See Diaconow, 1867a, 1867b, 1868b; Strecker, 1868; Bergell, 1900; Cousin, 1903; Henriques and Hansen, 1903; Laves, 1903a, 1903b; Wintgen and Keller, 1906; Erlandsen, 1907; Stern and Thierfelder, 1907; Fränkel and Bolaffio, 1908; MacLean, 1908b, 1909b, 1909c; Serono and Palozzi, 1911; Riedel, 1912; Trier, 1912, 1913b.)

Armand Manasse's (1906) determinations of the amount of lecithin obtainable from egg-yolk by different treatments show results nearly enough alike (range, 8.856-9.96 percent) to give considerable support to the average figure, 9.41 percent. Serono and Palozzi (1911) give 11.05 and 12.09 as the minimum and maximum percents of lecithin in fresh yolk. Tornani (1909) says that the amount of lecithin, and the relation between cholesterol and lecithin in egg-yolk is quite variable, that this relation changes as the eggs are kept, and is different in fertilized and unfertilized eggs. The amount found by Mesernitzy (1907) in fresh eggs was 15.35 percent of the dry substance, and the amount fell to about one-half of that by 20 days' incubation. Glikin (1908a) thinks that the eggs of those species of birds which are least capable of independent existence when hatched contain a larger supply of lecithin than others.

Distinctions have been made of several different phosphatids in egg-yolk. Laves (1903a, 1903b) states that there are several lecithins present, and that they are largely free, but partly in combination with protein and perhaps partly with cerebrin.

Henriques and Hansen (1903) found that changes in the character of the fat of the food did not lead to much alteration in the iodine number of the lecithin, though it did in that of the egg fat. The lecithin, then, seemed to retain its constancy of composition independent of the food fat. Barbieri (1910, 1912) made an examination of the extracts of egg-yolk usually said to contain lecithin, and came to the conclusion that the yolk contains no lecithin, either free or combined, that is, that there was no choline and no phosphorus united to glycerol. The phosphorus was said to be dialyzable, and all or in part in the form of soluble phosphates. We have not seen confirmation of this conclusion.

Stern and Thierfelder (1907) found three distinct phosphatids in egg-yolk: the first, orange red, was thought to be lecithin; the second, bright yellow, resembled cephalin; and the third, white, was apparently a diamino-monophosphatid. MacLean (1908b, 1909b, 1909c) reports a monamino-diphosphatid, and Fränkel and Bolaffio (1908), a triamino-monophosphatid, neottin.

Eppler (1913) separated two phosphatids from egg yolk. They differ in solubility in alcohol, and in the proportion of nitrogenous base (choline) which is present.

OTHER PHOSPHORUS-CONTAINING COMPOUNDS REPORTED PRESENT IN EGGS

The substance to which von Bunge (1885a) gave the name haematogen, and which he and Hugounenq and Morel (1905a, 1905b) examined with especial view to its being of the nature of an embryonic haemoglobin was found to be a pseudonuclein which may have been derived from the vitellin.

The mucoid present in egg, ovomucoid, has been supposed by some to contain phosphorus (see Milesi, 1898), but if carefully prepared there is not more than a trace of phosphorus (Langstein, 1903).

PHOSPHORUS IN THE DIGESTIVE SECRETIONS

GASTRIC JUICE

In the gastric juice which Schoumow-Simanowsky (1893-94) took by stomach fistulae from healthy dogs, phosphoric acid was found to the extent of 0.00398 and 0.0036 percent.

Pekelharing (1902) believes pepsin to be free from phosphorus, and that the phosphorus which others have found in their preparations was present as a contamination of lecithin or perhaps a phosphorus-containing mucus. Pekelharing mentions Nencki and Sieber as believing that there is a nucleoprotein in the gastric juice.

PANCREATIC JUICE

Pancreatic juice, caused to flow from dogs by the introduction of secretin, is reported by Plimmer and Kaya (1909) as showing the following distribution of phosphorus compounds.

DISTRIBUTION OF PHOSPHORUS IN DOGS' PANCREATIC JUICE
Plimmer and Kaya (1909) Percent of Total P_2O_5

Dog	Ether soluble P_2O_5 (lecithin)	Water soluble P_2O_5 (nucleic acid and inorganic)	Inorganic P_2O_5	Protein P_2O_5 (nucleoprotein and phosphoprotein)	Phosphoprotein P_2O_5
I	0	56 3	Present	43 7	43 7
II	0	86 3	Trace	13 7	13.7
III	0	59 8	Trace	36 7	40.2

Frouin and Gérard (1912) determined the phosphorus in the pancreatic juice of the cow and the dog. Pancreatic juice was obtained from dogs having temporary fistulae by the injection of secretin. From 7 animals 1700 c.c. of the juice was collected in 6-7 hours. It contained 0.006 gm. P per liter. From cows with permanent fistulae the pancreatic juice contained 0.0089 gm. P per liter; the juice as collected a month later by catheter in the pancreatic duct contained 0.003 gm. P per liter.

BILE

The phosphorus-containing constituents of bile are phosphatids and a very little mineral phosphate. The mucus of the liver secretion is said to be either nucleoalbumin or nucleoprotein (Paijkull, 1888). The inorganic constituents of bile are the chlorides of sodium and potassium and small amounts of the phosphates of calcium, magnesium and iron. Edlefsen (1880) taking the old formula for haemoglobin, which gives it a phosphorus content, worked out a reaction by which the haemoglobin of the red corpuscles disintegrating in the liver may furnish a part of the phosphorus of bile, a part going to the urine.

The phosphatids in general are, of course, usually spoken of, in all but the more recent writings, as lecithin, but it is shown (Hammarsten) that there are in bile phosphatids of different solubility and different relation of N:P. Hammarsten found evidence of a jecorin-like phosphatid, in certain cases at least. The first finding of lecithin in bile was apparently that of Gobley (1856). It was then detected by the presence of oleic acid and margaric acid in some kind of combination not a fat. Quantitative determinations of the lecithin have commonly been simply by computation from the phosphorus found in the ether extract.

Hammarsten (1901, 1902, 1904, 1905b) made a study of the bile of different species of animals, especially those of polar regions. He notes that the largest amount of lecithin is in the bile of the polar bear which uses a diet unusually rich in fat, and thinks it may be Nature's provision for the digestion of the fat. In the table the animals are arranged in order of decreasing phosphatid content

of the bile. The bile of the liver and that of the gall bladder are said not to be alike in composition, the lecithin being considerably higher in the bladder bile.

PHOSPHORUS FOUND IN THE ETHER EXTRACT OF THE BILE OF VARIOUS ANIMALS—(Hammarsten, 1905)

Animal	Phosphorus in ether extract Percent P	Lecithin computed from the same Percent
Polar bear	0 911-1 14	23 12-28.96
Man (bladder)	0 048-1.17	1.23-29.75
Man (liver)	0.100-0 611	2.54-15.5
Dog	0 768	19.50
Brown bear	0 502	12.74
Orang-outang	0.420	10.67
Hog	0.334	8.47
Python	0 332	8 43
Sheep	0 289	7 35
Musk ox	0 272	7.04
Hippopotamus	0.191	4.86
Cattle	0.181	4.60
Seal	0.168	4 27
Goose	0.162	4 10
Walrus	0.043	1 08
Sea wolf	0.033	0.81
Codfish	Present but too little to be determined	

Daniel-Brunet and Rolland (1911b) reported certain chemical analyses of the bile and the liver of cattle. The following table shows the range of the values found for compounds of phosphorus.

PHOSPHATES, NUCLEOPROTEINS AND LIPOIDS OF BILE OF CATTLE
Parts per 1000

	Phosphates P_2O_5		Nucleo-proteins		Lipoids					
					Total		Cholesterins		Lecithins and neutral soaps	
	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.
Bile	1.31	1.58	1.15	2.25	1.100	2.130	0.410	0.813	0.690	1.317

In another article (1911a) these authors say that, with cattle, neither sex nor castration was found to make any difference as to the quantity of the mineral elements, the glycogen or the nitrogenous compounds in the bile; but they did affect the lipoid content, bulls showing the most lipoids, cows less, and steers still less.

Rosenbloom (1912, 1913b) reports the following analysis of human bile taken from a biliary fistula, as parts per 1000; total solids 29.8, bile salts 10.1, mucin and pigments 4.86, cholesterol 2.61, fat 6.85, soaps 2.6, lecithin 6.42, inorganic matter 9.2, fatty acids 1.2.

See also Brand (1902), Yeo and Herroun (1884-5), Baginsky and Sommerfeld (1895), Pruszyński and Siemieński (1906), Bonanni (1906), and Long and Gephart (1908b).

SALIVA

The saliva contains phosphates. With regard to the quantitative relations of the mineral constituents of the saliva, the following data are at hand:

Hammerbacher (1881) made an organic and inorganic analysis of mixed human saliva in which the inorganic salts formed 2.205 parts per 1000. The ash analysis was as shown below:

	Percent
K_2O	45.714
Na_2O	9.593
CaO (with trace of iron oxide)	5.011
MgO	0.155
SO_3	6.380
P_2O_5	18.848
Cl	18.352
	104.053
Oxygen equivalent of chlorine	4.135
	99.918

By computation from the ash analysis, it was concluded that the ash of the saliva may have been made up of the following compounds:

Compound	Percent
KCl	38.006
K_2SO_4	13.908
K_3PO_4	21.278
Na_3PO_4	16.917
$Ca_3(PO_4)_2$	9.246
$Mg_3(PO_4)_2$	0.338
	99.693
Excess Cl	0.282
	99.975

This aggregates 90.109 percent alkali salts and 9.584 percent alkaline earth phosphates. Hammerbacher says that Enderlin found 92.367 percent alkali salts and 5.509 percent earth phosphates with a trace of iron phosphates.

Schäfer's "Text-Book of Physiology," Vol. I, p. 348 quotes from Jacubowitsch, through Hermann's "Handbuch," V (2), p. 14, the following analyses of the ash from mixed saliva, expressed as parts per 1000 parts of saliva.

	Human	Dog
Total solids	1.82	6.79
Phosphoric acid	0.51	0.82
Soda	0.43	
Lime	0.03	0.15
Magnesia	0.01	
Alkaline chlorides	0.84	5.82

Schäfer also quotes (p. 347) from Herter, through Hoppe-Seyler, "Physiol. Chem.," II, p. 191, the following as the salts found in submaxillary saliva, expressed as parts per 1000 of saliva:

K_2SO_4	0.209
KCl	0.940
NaCl	1.546
Na_2CO_3	0.902
$CaCO_3$	0.150
$Ca_3(PO_4)_2$	0.113

F. N. Schulz gives, in Oppenheimer's "Handbuch der Biochemie des Menschen und der Tiere," III, p. 29, the following ash analyses from Jacobi (Diss., Würzburg, 1896):

	Percent I	Percent II
Cl	14.46	13.68
K	35.88	35.69
Na	32.91	21.61
P_2O_5	10.98	17.70
Sulphuric acid	Trace	7.1
Ca	2.19	3.96
Mg	0.47	0.69

Barillé (1911) considers that dental tartar is derived from the saliva through the precipitation of its salt as tricalcic phosphate and calcium carbonate as a result of the loss of carbon dioxide from the carbonophosphate in the saliva. Barillé found in the inorganic part of tartar 70 percent of the phosphate and 8 percent of the carbonate of calcium.

Roger (1908) believes that the presence of phosphates is necessary for the amylolytic action of saliva. He showed that the sugar-forming power of saliva may be destroyed by precipitation of the phosphates with uranium acetate, and restored by addition of sodium phosphate.

PHOSPHORUS PRESENT IN CHYLE

Hamill (1906-07) collected chyle through a fistula in the thigh of a human subject, and examined it for various constituents. The lecithin averaged 4.204 gm. per 100 gm. of ether extract. Lipase and amylase were both present. Lecithin given by mouth during the time of observation produced a rise in the ether-soluble phosphorus of the chyle.

PHOSPHORUS PRESENT IN LYMPH

From the few phosphorus estimations on lymph which have come to our attention we are unable to conclude as to its usual content. Odenius and Lang (1874) found 13 parts per 1000 of soluble P_2O_5; E. Ludwig (quoted by von Zeynek, 1895) found 15 parts total P_2O_5 per 1000; von Zeynek (1895) found 0.095 parts soluble, and 0.214 parts insoluble P_2O_5 per 1000 c. c., while Zaribnicky (1912) found in the lymph of the horse 0.089 parts total P_2O_5 per 1000. The preceding figures were from analyses of human lymph. See also Dähnhardt (1866).

PART IV

NORMAL PHOSPHORUS METABOLISM

MAINTENANCE OF NEUTRALITY

The approximate constancy of reaction of the body fluids, which is one of the conditions essential to life, is maintained at neutrality (actually very slight alkalinity) by a group of counteracting agencies prominent among which are the phosphates.

The need for such an adjustment is due to the facts that the predominating chemical reaction of the body is the oxidation of carbon compounds to carbonic acid, and that sulphuric and phosphoric acids are prominent among the normal products of protein katabolism.

This control of reaction in the body fluids is accomplished by phosphates, carbonic acid and carbonates, aided by the amphoteric proteins, and sustained by the excretory functions of the lungs for carbonic acid, and of the kidneys and intestine for phosphates.

We shall consider in detail only Henderson's theory of the peculiar effectiveness of carbonic and phosphoric acids and their salts in this adjustment. (Henderson, L. J., 1906, 1098a, 1908b, 1908c, 1909, 1911, 1913; Henderson and Black, 1907, 1908; Fitz, Alsberg and Henderson, 1907.) Henderson's explanation of this phenomenon is based on physico-chemical considerations and ion concentration measurements. The substances considered are the two pairs of compounds, carbonic acid and bicarbonate, and the mono- and di-phosphate. The processes concerned may be represented by the two equations,

$$M_2HPO_4 + HA \rightleftarrows MA + MH_2PO_4$$
$$MHCO_3 + HA \rightleftarrows MA + H_2CO_3$$

where M stands for any basic radical; A, for any acid radical. The indications are that in the fluids of the body the carbonic acid is present as carbonic acid (H_2CO_3) or sodium bicarbonate ($NaHCO_3$), and all of the phosphoric acid as mono-sodium phosphate (NaH_2PO_4) or di-sodium phosphate (Na_2HPO_4). Now, mixtures of these compounds in solution possess greater power than any other known salts for balancing each other, and any acid or base that may be added, so that the solution remains neutral. While a pure solution

of NaH_2PO_4 is very weakly acid, and one of Na_2HPO_4 is very weakly alkaline, one of a mixture of the two adjusts itself by ionization so that it is neutral; and addition of an acid to such a solution does not give it even the slight acidity of mono-sodium phosphate till enough acid has been added to convert all of the di-sodium salt to mono-sodium salt. Bases produce an opposite effect, but will not give the mixture even the faint alkaline reaction of di-sodium phosphate till all has been converted to that form.

The case is similar for carbonic acid and bicarbonates, and when all four compounds are present in a solution, the base distributes among these components so that the relative amounts of each are constant for any given temperature.

By mathematical deductions Henderson shows that the strength of an acid theoretically best fitted to preserve neutrality in a pure solution is such that its ionization constant is near 1×10^{-7}, which is the ionization constant of distilled water; or, more exactly, "that its ionization constant, divided by the degree of ionization of its salt, is precisely equal to the hydrogen ion concentration in pure water." The ionization constant of H_2CO_3 is 3×10^{-7}, and that of the $H_2PO_4^-$ ion is 2×10^{-7}. Hence both of these are theoretically, as they are found to be practically, nearly ideal neutralizing agents near the neutral point.

The condition to be maintained, however, is not exactly the neutrality of distilled water, and at the alkalinity required very slight variations in hydrogen ion concentration are accompanied by greater variations in sodium bicarbonate content than in the ratio of mono- and di-sodium phosphate. Hence the carbonate is more efficient than the phosphate, proportionately, in maintaining alkalinity. The concentration of bicarbonate is then from ten to twenty times the concentration of carbonic acid, and neutrality is attained only when the concentration of bicarbonate has fallen nearly to that of the carbonic acid. This efficiency of the bicarbonate-carbonic acid equilibrium is further increased by the maintenance of a nearly constant supply of carbonic acid through its removal by the lungs.

The phosphates, however, have certain other advantages. At the most critical point, that is, when the bicarbonate is nearly used up and the system is very near the neutral point, the phosphates are most effective. Furthermore, they are present, especially in protoplasm, probably in much greater amounts than the carbonate, and are correspondingly of greater service. In addition, the easy diffusibility of acid phosphates and their removal by the excretory organs must greatly enhance their practical efficiency.

With regard to the magnitude of the effect of these two agents together in the protoplasm, Henderson says: "Only when an amount of acid equal to about three-fourths of the total carbonic acid plus the total phosphoric acid of the protoplasm has been added to the protoplasm can there be a real beginning of acidity."

This mechanism of equilibrium in the tissues and fluids very greatly reduces the alkali requirement of the body; but it must be sustained, as it is, in fact, by special retention mechanisms at the points of excretion, by means of which the alkalis are returned to the blood after the excretion by lungs and kidneys of acids with which these bases were combined.

In so far as the alkalis are united with carbonic acid they are entirely saved to the body, as the carbonic acid leaves the body in the gaseous state through respiration. The amount of alkali in use in this way is said to be about 1.5 gm. at any moment, or 400 gm. per day.

Alkalis are, however, removed from the body in the urine of omnivora and carnivora, chiefly as phosphates and sulphates. At the kidney there are two provisions, probably about equal in their effect, for sparing alkali. First, the fixed alkalis are replaced by ammonia, in so far as it is available. This is all clear gain of base, because the ammonia comes from nitrogenous compounds which are nearly neutral, and if completely oxidized becomes neutral urea. The other factor which saves alkalis to the body is the physico-chemical process by which acid urine is separated from the alkaline blood. Though the change of reaction is small, the amount of base involved may be considerable in the presence of phosphates and other salts and acids having the ability to undergo wide variation in the amount of base which they hold with but slight variation in hydrogen ion concentration. As we have already noted, phosphates are peculiarly effective in this way near the neutral point. Carbonic acid and uric acid have the same property, and, at hydrogen ion concentrations such as are reached in acidosis, the β-oxybutyric acid and its salts, which are then present, are also effective in the same way.

With regard to the relative magnitude of the parts played by the proteins, the bicarbonates and the phosphates in maintaining neutrality nothing definite can be asserted, nor can it be said that there are not other unrecognized agencies involved. Conditions within the body cannot be exactly duplicated outside, especially as to the influence of colloids; but as far as true solutions are concerned quantitative measurements can be made with pure substan-

ces which give some idea of the possible degree of effectiveness of the different agents; and the final word in the discussion between T. Brailsford Robertson and Lawrence J. Henderson (Robertson, 1909b, 1910a; Henderson, L. J., 1908a, 1908c, 1909) seems to be that, so far as the blood is concerned, in passing from the reaction of normal blood to that of blood in advanced acid intoxication, the proteins of the blood are about one-fifth as efficient as the bicarbonates in maintaining its neutrality. In the tissues or tissue-fluids the proteins very likely play a larger part. Henderson attributes a relatively greater effectiveness to bicarbonate than to phosphate except at points very near to neutrality.

Michaelis (1913) gives the average H^+ ion concentration of human venous blood, in normal resting condition, as 2.75×10^{-8} at 20-21° and 4.46×10^{-8} at 37.5°; and the greatest variations from this mean, found under such conditions, amounted to +12 and —11.7 percent of the mean. A difference of ±6 percent is attributable to uncertainties of the method of determination, so that the variations observed are but very slightly beyond the limits of error of work.

THE ABSORPTION AND ELIMINATION OF COMPOUNDS OF PHOSPHORUS

GENERAL CONSIDERATIONS

After the ingestion of ordinary food, with its variety of phosphorus compounds, organic and inorganic, there begins at once the same process of simplification and absorption that is general for other groups of its nutrient components. The inorganic phosphates are, of course, absorbed as such. The organic phosphorus compounds are absorbed in part without change, in part after partial cleavage, and in part after complete separation into their simplest groups, with the liberation of phosphorus as inorganic phosphoric acid, the method differing with the nature of the nutrient. The phosphoric acid split off from organic compounds during digestion behaves just as does any other inorganic phosphoric acid introduced as such (Oeri, 1909). The larger part, though by no means all of the food phosphorus, therefore, is absorbed as inorganic phosphate. For details as to the digestion of the several groups of phosphorus compounds see the special discussions of these groups.

Such inorganic phosphates as are insoluble in water are most of them readily soluble in the hydrochloric acid of the gastric juice. They are then absorbed, mainly in the small intestine, which is usually faintly acid in the upper portions (Raudnitz, 1893; and Wuertz, 1912).

It is usually said to be true that absorption of phosphates takes place only in the acid portion of the small intestine, but von Wendt and Zuckmayer, as noted below, suggest means by which phosphates may be absorbed from the alkaline portions of the alimentary tract.

Since the phosphorus of the food is mostly in completely oxidized forms there can be no significant change in the state of oxidation during metabolism. There is evidence of some capacity, however, for animals to oxidize the less completely oxidized compounds, as is observed by Heffter (1903), who states that in the healthy organism phosphorous acid is completely oxidized. He states, also, that pyrophosphates and hypophosphites are excreted unchanged, while metaphosphates are changed to the ortho- form.

The circumstances which determine whether phosphates shall be eliminated through the urine or the feces are first, the reaction of the contents of the alimentary tract, as determined especially by hydrochloric acid and carbonates; second, the nature and relative amounts of the other mineral elements, especially the bases, present in the digestive tract, as affecting the solubility of the phosphates; third, after the absorption of the phosphates from the alimentary tract, all of those circumstances which control the secretion of phosphates into the digestive tract and the reabsorption from the same; fourth, the many circumstances which affect the reaction of the blood serum and the amounts and proportions of the other salts present, as affecting the form and therefore the solubility of the phosphates, the more readily soluble tending to go out through the urine; and fifth, the species of animal involved.

There may be a considerable variation as to path of outgo without apparent change of conditions; thus the experiments of Kochmann (1911) (see Infl. of Amount of Food on P. Met.) show that on the same amounts of the same kind of food there may be a change of urine phosphorus from 27 to 34.9 percent of the total outgo, and of feces phosphorus from 65.1 to 73 percent of the total outgo, without apparent cause.

This whole problem, then, is almost hopelessly complicated, though we are able to record a considerable number of harmonious observations as to the bearing of certain individual factors.

The general course of the minerals during their passage through the alimentary tract has been traced by Wildt (1874, 1879), who made a study of digestion in sheep by analyses of the contents of the different parts of the alimentary tract. By means of quantitative estimations of the silica and also the absorbable constituents of the food, in each part of the tract, it was possible to trace absorption, to recognize both the organic and inorganic constituents of

each of the digestive secretions, and later to tell where, when, and to what extent these constituents were again absorbed and returned to the blood stream.

The amount of phosphorus secreted into the alimentary tract was, in each of the three sheep studied, greater than the total amount in the food. Secretion of phosphorus greatly exceeded absorption in the first and second stomachs, but was less than absorption in the third stomach; changed again so that secretion exceeded absorption in the abomasum and duodenum, and once more so that absorption exceeded secretion in the remainder of the tract.

The principal secretion of phosphorus was in the saliva and in the secretion of the abomasum, and its largest absorption was from the small intestine. Calcium and magnesium, on the other hand, were secreted principally into the small intestine, and were absorbed most actively from the first and second stomachs and the colon.

The following tables set forth the facts as Wildt determined them as to the absorption and secretion of phosphorus and the mineral bases.

ABSORPTION AND SECRETION OF PHOSPHORUS, CHLORINE AND THE MINERAL BASES IN THE ALIMENTARY TRACT OF THREE SHEEP—Grams

		First and second stomachs	Third stomach	Abomasum and duodenum	Small intestine	Caecum	Colon	Large intestine	
								Entire	Last part
K	Sheep I	−2.525	−2.232	+1.665	+3.746	−7.436	−0.391	−0.186	+2.178
	" II	+1.993	−4.811	+5.218	−4.714	−3.321	−1.607	0.525	+0.761
	" III	−2.104	−2.480	+9.683	−6.955	−2.073	−0.903	−1.042	−0.912
Na	Sheep I	+14.794	−10.004	+2.983	+15.871	−14.837	−3.527	−3.560	−3.179
	" II	+15.673	−10.167	+7.167	+7.060	−12.566	−1.746	−3.086	−1.703
	" III	+13.006	−6.389	+20.715	−1.687	−17.728	−2.967	−3.740	−1.935
Ca	Sheep I	−0.729	+0.163	−1.284	+1.415	+0.653	−1.023	+0.555	−0.424
	" II	−0.236	+0.214	−0.803	+0.118	+0.396	−0.686	+0.107	−0.386
	" III	−1.002	+0.278	+0.536	−0.328	+0.754	−0.585	+0.050	+0.198
Mg	Sheep I	−0.675	−0.316	+0.109	+0.719	−0.175	−0.479	+0.022	+0.207
	" II	−0.472	−0.128	−0.129	+0.557	−0.235	−0.274	−0.289	+0.311
	" III	−0.724	−0.189	+0.596	−0.199	+0.328	−0.278	+0.089	−0.010
P_2O_5	Sheep I	+7.359	−2.068	+0.155	+3.470	−7.348	−0.523	−0.707	+0.980
	" II	+9.064	−2.861	+2.818	−2.164	−5.175	−0.642	−0.290	−0.353
	" III	+5.416	−1.091	+8.939	−8.701	−2.440	−0.437	−0.416	−0.556
Cl	Sheep I	−1.284	+0.925	+12.835	−1.687	−9.558	−1.209	−1.491	−0.828
	" II	+1.821	−1.425	+18 ?	−10.619?	−7.167	−0.150		−2.174
	" III	−1.538	−1.012	+27.422	−16.032	−9.584	−1.389	−1.141	

(−)=more absorbed than secreted. (+)=more secreted than absorbed.

SECRETION DURING TWENTY-FOUR HOURS IN VARIOUS PARTS OF THE ALIMENTARY CANAL—Grams

	Mouth (Saliva)	Abomasum	Small Intestine	Total	Daily Food
K		4 443		4 443	9.078
Na	15.010	7.291	9 270	31 571	1.103
Ca			0 601	0.601	3.267
Mg					
Cl		17.240		17.240	3.162
P_2O_5	7.969	2.584		10.553	0.966

One point which a study of these tables makes clear is the utter absurdity of the usual statements as to digestibility of mineral nutrients, and also of many statements as to coefficients of absorption of inorganic salts.

The mineral salts, including phosphates, reach the general circulation almost wholly through the portal system. The final disposition of the phosphates under ordinary conditions of nutrition may then involve retention in the body, or elimination, either in urine or feces. There are also the various losses of phosphorus involved in reproduction and lactation. It would seem from the work of Taylor (1911) that there is no cutaneous elimination of phosphates. Taylor studied the cutaneous elimination of nitrogen, sulphur and phosphorus with two laboratory assistants in periods of 28 and 45 days. The average daily cutaneous eliminations were as follows:

Substance	Subject J.	Subject D.
	Grams	Grams
S	0 028	0 015
P	0 003	0 002
N	0.190	0.160

The author concluded that the phosphorus figure stands for desquamation only, and that there is not a real cutaneous elimination of phosphorus in any form.

In discussing urinary and feces excretion of calcium salts, VonWendt (1905) suggests that the acidity of the urine is responsible for its content of calcium salts, while the calcium salts which are excreted into the intestine are rendered more or less insoluble by the alkalinity of the intestinal juices, their reabsorption being thereby restricted. Phosphates are supposed to be excreted into the intestine as mono- and di-salts. Here the di-salt decomposes into mono- and tri- salts, and the latter, further, with the taking up of the elements of water, into basic phosphate and acid. Since, of these phosphates, only the mono-salt can be considered as relatively easily soluble in the weakly alkaline intestinal juice, their reabsorption takes place principally in this form, though to some extent also as the di-salt. From the relation of Ca:P in the feces vonWendt concludes that the calcium is present as the trimetallic phosphate.

Zuckmayer (1912) found that "tricalcol," an alkali-soluble colloidal calcium preparation, was absorbed from the small intestine of a rabbit and a dog, while the tricalcium phosphate, directly introduced, was not usually absorbed. Zuckmayer states that in normal digestion calcium (calcium phosphate) is withdrawn from food

substances by the acid of the stomach, with the formation of acid calcium phosphate and calcium chloride, and probably also phosphoric acid in the presence of protein cleavage products. He also suggests that in the small intestine, as soon as there is sufficient alkali present, the dissolved calcium phosphates are again changed to tricalcic phosphate, which becomes absorbable through the agency of the colloidal protein cleavage products.

In studying the conditions governing calcium and phosphorus metabolism in infants Blühdorn (1912-13) experimented with calcium and phosphorus compounds added to feces extracts *in vitro*. If to 8 c.c. of distilled water were added 1 c.c. each of N/50 Na_2HPO_4 and N/100 Ca Cl_2 a slight but distinct precipitate of $Ca_3(PO_4)_2$ appeared. By similar addition of these salt solutions to water-extracts of feces it was determined that if Ca salts occur with phosphates in the intestine, in weakly acid or alkaline reaction, insoluble $Ca_3(PO_4)_2$ results, and in this way Ca and P may be withdrawn from absorption. A strong acid reaction prevented the precipitation of $Ca_3(PO_4)_2$. The colloids of the feces extracts appeared to play no decisive role in these processes.

Plimmer (1913a) studied the action, on phosphorus compounds, of enzymes obtained from pancreas, liver, intestine, castor beans, yeast and wheat bran. The phosphorized nutrients studied included glycerophosphoric acid, phytic acid, nucleic acid, casein and others. The most active tissue in the hydrolysis of the organic phosphorus compounds was thought to be the intestinal mucous membrane. Phytic acid was attacked readily only by an enzyme in the bran extract. Casein was the only one of these compounds which was hydrolyzed by the pancreas extract. From the activity of the intestinal mucosa in the cleavage of organic phosphorus compounds Plimmer concludes that they are absorbed only in the hydrolyzed condition, the phosphorus as inorganic phosphate. The lipoclastic enzymes were shown not to be active in the hydrolysis of organic phosphorus compounds.

While Plimmer's conclusion as to the absorption of phosphorus compounds only in a state of hydrolytic cleavage is doubtless true of the bulk of the phosphorus absorbed from organic compounds, his evidence is not of such nature as to controvert successfully the established facts as to the absorption of a part of the organic phosphorus of the food in unsplit or incompletely hydrolyzed forms.

THE INFLUENCE OF PHOSPHATES ON DIGESTION

The nature of the influence of phosphates in digestion was shown by Berg and Gies (1906-7), who studied the effects of ions on catalysis, with especial reference to peptolysis and tryptolysis. The H^+ ion is the favorable factor in peptolysis, and the OH^- ion in tryptolysis; the associated ions, or molecules, or both, exerting deterrent influences in variable degrees. Variations in swelling effects on fibrin, in general, correspond to these digestive differences.

Finzi (1903) determined that intravenous injection of neutral sodium phosphate caused increased secretion of saliva, and increased phosphate content of the saliva.

Ferrata and Moruzzi (1907) determined that a phosphorus-containing food causes an increase in the lecithin content of the intestinal mucous membrane of the dog, while the nucleoproteids were increased after the taking of food of any kind.

Roger (1908) found that the amylolytic power of the saliva decreased with the addition of uranium acetate, and disappeared with the complete precipitation of the salivary phosphates. The addition of sodium phosphate then caused the amylolytic action to reappear. Conclusions were sustained by adequate numerical data.

Giacosa and Dezani (1909) found phosphates in the press-juice from pig stomach, but also prepared from it a phosphorus-free digestive enzyme.

A. Loeb (1910) showed with a dog that the urinary phosphorus was reduced, temporarily, by the taking of food, apparently because of its utilization in the preparation of the digestive juices.

Lisbonne (1911) reports that phosphates do not activate salt-free amylases of the saliva and pancreatic secretion as do chlorides.

W. Löb (1911) demonstrated that phosphates stand in an important relation to the utilization of sugar. Glycolysis, which is favored by hydroxyl ions, is accelerated by the presence of phosphate ions; with constant hydroxyl ion concentration, the acceleration rising with the absolute amount of phosphate present. Lecithin or glycerophosphates hinder phosphate glycolysis.

The activating effect of primary and secondary phosphates on various proteases is compared by Fernbach and Schoen (1911).

The above notes show that phosphates stand in such a significant relation to the digestion and utilization of food that their excretion into the alimentary tract must be regarded as of vital consequence.

The possible significance of phosphates in relation to enzymatic processes in animal bodies is indicated by a series of studies by Wróblewski, Harden, Young, and Euler and associates, on the relation of phosphates to the enzymes of yeast.

Wróblewski (1901) demonstrated the favorable effect of a certain concentration of phosphate on the action of zymase from yeast press-juice. Harden and Young (1906, 1908a, 1908b, 1909, 1910, 1911a, 1911b) also found that phosphate accelerates the fermentation of sugar by yeast juice, the phosphate becoming non-precipitable by magnesia mixture. Young (1907, 1909, 1911) shows that the organic phosphorus compound above mentioned is a hexose phosphate. The method of action of the enzyme involved, phosphatese, is discussed in a series of papers by Euler and Kullberg (1911), Euler and Ohlsén (1911), Euler and Lundeqvist (1911), Euler and Ohlsén (1912), Euler (1912a) and Euler and Bäckström (1912). Other studies on the influence of phosphates on the enzymes of yeast are those of Euler and Beth af Ugglas (1911).

AUTOLYSIS OF COMPOUNDS OF PHOSPHORUS

The intermediary metabolism of phosphorus is accomplished through the agency of enzymes. Given the particular conditions necessary for their activity, they are able to bring about the various changes in the state of organization of matter which are essential to the maintenance of life. Our state of knowledge of these compounds is especially incomplete, and we make no effort to present a full discussion of the subject. We merely offer a few notes on investigations demonstrating the existence of such compounds, and the nature of the cleavage which they may induce; and we make the suggestion that reversibility of direction is a not infrequent characteristic of enzyme action, some at least of the autolytic enzymes undoubtedly possessing, with change of conditions, capacity for synthesis in the same field of activity. Evidence of the activity of autolytic enzymes has been accumulated by a great number of workers, among whom are those whose names follow, these having given attention to compounds of phosphorus.

Kutscher and Lohmann (1903) found no autolytic decomposition of the lecithin of the brain of the ox, but Coriat (1904a) found an enzyme in brain tissue capable of splitting choline from lecithin. This enzyme acts only in neutral or slightly alkaline media, and the yield of choline is greater in the latter than in the former.

Satta (1907, 1908) determined that both lecithin and nuclein phosphorus in ox liver, pancreas and thymus split off inorganic phosphorus in autolysis, the nuclein more rapidly than the lecithin. Below are data from this study:

THE AUTOLYSIS OF ORGANIC PHOSPHORUS COMPOUNDS
Satta (1907, 1908)

Organ	Animal	Total phosphorus as P_2O_5 Percent	Percents of total phosphorus			Duration of autolysis Days
			Alcohol-ether-soluble (Lecithin, jecorin, etc.)	Water- and acetic acid-soluble (Inorganic)	Freed by ashing (Nuclein)	
Liver	Ox	2.9	30.60	31.79	37.61	..
Liver	Ox	2.8	28.2	51.8	20.0	2
Liver	Ox	2.7	25.20	62.95	11.85	7
Liver	Ox	2.65	23.60	66.46	9.94	12
Liver	Ox	2.89	21.61	69.9	8.49	21
Pancreas	Ox	3.87	41.69	22.71	35.60	..
Pancreas	Ox	3.23	34.20	60.50	5.30	1
Pancreas	Ox	3.47	11.47	84.73	3.80	5
Thymus	Calf	3.9	10.95	20.05	69.00	..
Thymus	Calf	4.0	9.56	24.27	66.17	1
Thymus	Calf	3.8	9.26	43.72	47.02	3
Thymus	Calf	3.8	9.1	51.75	39.15	10
Thymus	Calf	3.8	9.0	59.46	31.54	30
Lymph, sarcoma of intestine	Man	1.85	19.66	39.59	40.75	..

Satta and Fasiani (1910) determined that the presence of lipoids increased the autolysis of liver, as measured by the amount of nitrogen passing into solution in a given time. The action seemed to be most pronounced when the liver of a starved animal was used for the autolysis. The action was not proportional to the amount of lipoids present.

Simon (1911) demonstrated active autolysis in brain tissue, which affected not only the phosphorus compounds soluble in alcohol and ether, but also those which are insoluble, the proportion of the former to the latter, represented by the inorganic phosphorus split off from organic compounds, being as 61 to 39.

Grund (1912a, 1912b, 1913) determined that in degenerating muscle, following the division of its nerves, there occurs a large increase of fat, and of water in proportion to fat-free substance; but in the dry, fat-free substance the total nitrogen, total phosphorus and phosphatid phosphorus remain constant. On the other hand, the ratio of protein phosphorus to total phosphorus greatly increases, as also the ratio of protein phosphorus to protein nitrogen. Thus the protein phosphorus maintains its integrity, while phosphorus-free proteins dissolve. Degeneration as caused by hunger is accompanied by the katabolism of all the protein components.

For a discussion of autolysis of the several groups of organic phosphorus compounds see the discussions of the metabolism of the same.

METHOD OF URINARY ELIMINATION OF PHOSPHATES

In view of the importance of the function of the kidneys in freeing the system from certain classes of katabolites, and thus assisting in the maintenance of that constancy of conditions in the

blood which is essential to the vital functions, it is a matter of interest to know the method of formation of urine and the agencies through which this is accomplished.

M. Maly (1876) shows that acid constituents diffuse and dialyze more rapidly than alkali from such mixtures as are found in the blood, this depending on the greater mobility of ionized hydrogen, and of more complex substances which contain hydrogen, than of corresponding basic substances. Thus acid phosphates are separated from alkaline blood.

This theory receives support from the investigation of Fitz, Alsberg and Henderson (1907), who demonstrated by hydrochloric acid feeding to rabbits that the resultant shifting of the salt equilibrium toward the acid side increased the urinary elimination of phosphates.

In harmony also with this idea is the observation of Teissier (1877) of inverse relations in the excretion of glucose and phosphates, the significance of which probably lies in an accentuation of the state of acidosis during diminished glucose outgo.

Liebermann (1893b) found that alkaline solutions passed through a filter of lecithalbumin become acid. He therefore advanced the theory (with experiments) that acid urine may arise in such a way, by the acid bodies in the kidney cells removing base from alkaline urates as the urine passes, provided there is not too much alkali.

Frey (1911) also investigated the nature of the process by which phosphorus is separated from the blood in the kidneys. By intravenous injection of Na_2HPO_4, and phosphorus determinations on the blood serum and urine, he found that the urine contained from 10 to 60 or 70 times the concentration of phosphorus that exists in blood serum; thus it appears that the process of separation of phosphorus from the blood in the kidneys is more than one of filtration.

Folin (1905) in discussing the laws governing the composition of the urine maintains the incorrectness of the usual view (see, for instance, G. Zuelzer, 1905 and Ott, 1886) that the phosphates of normal acid human urine are present to the extent of about 60 percent in the diacid form, and states that the phosphates of clear acid urine are all monobasic, the acidity of such urines being ordinarily greater than the acidity of all the phosphates, the excess being due to free organic acids.

It is Folin's idea that the precipitate with barium chloride which is ordinarily considered to include the diacid-phosphates in reality contains phosphorus only as an impurity in the abundant precipitate of barium sulphate.

According to Hammarsten (1911), p. 784, phosphorus may be found in urinary sediments as tricalcic and trimagnesium phosphates in alkaline urines, as dicalcium phosphate in neutral or faintly acid urine, and as ammonium magnesium phosphate in urines which have become ammoniacal through alkaline fermentation, or in amphoteric urines in the presence of a sufficient quantity of ammonium salts.

ORGANIC PHOSPHORUS IN THE URINE

From an early date it has been recognized that a portion of the phosphorus of the urine is present in organic combination. Ronalds (1846) considered that he found organic phosphorus in the urine, though he states that his methods were unsatisfactory.

Sotnitschewsky (1880) determined glycerophosphoric acid as a common constituent of human urine, though the amount present is sometimes very small.

W. Zuelzer (1881a) found that the urine of a man 22-25 years old contained 1-2 mg. of phosphorus (stated as P_2O_5) combined with glycerin. In fever no more was found, but much more was found after chloroform anaesthesia, subcutaneous injection of morphine, after the crisis of pneumonia, and in erysipelas. The maximum amount found by Zuelzer for 24 hours is 35 mg. P_2O_5.

Lépine and Eymonnet (1882) examined the urine of more than 100 subjects. Normal human urine they found to contain about 0.150 gm. of glycerophosphoric acid per liter, being about 0.15 to 0.3 of one percent of the amount of the nitrogen. With fatty degeneration of the liver in tuberculosis the value of the glycerophosphoric acid, in percent of nitrogen, was found to be 1.0-1.8, or about 6 or 7 times the normal.

In a later article (Lépine, Eymonnet and Aubert, 1884) they report increased proportions of unoxidized to total phosphoric acid in the urine in apoplexy, epilepsy and delirium tremens, and in a dog after subcutaneous injection of hydrochlorate of morphine, and also in a dog after the ingestion of potassium bromide. They state that in pernicious anaemia it may be present in four times the normal amount, without an increase in the total phosphorus. An excess above normal occurs also in some cases of icterus, typhoid fever and acute pneumonia; while in cases of meningitis the unoxidized phosphorus was present in less than the normal relation to the nitrogen of the urine.

Bülow (1894) found, with dogs, that the phosphoric acid esters of the urine did not vary greatly with the introduction, either *per os* or subcutaneously, of glycerophosphates, these salts, in so far as

they were excreted in the urine, being mostly decomposed to phosphates. His figures are as follows:

URINARY EXCRETION OF PHOSPHORIC ACID ESTERS BY DOGS

Days	H_3PO_4 as ether-phosphoric acid	
5	0.00619	Normal conditions
1	0.01085	3 gm. calcium glycerophosphate+2 gm. calcium carbonate *per os*
1	0.01191	3 gm. sodium glycerophosphate, subcutaneously
1	0.00626	Next day
1	0.00573	3 gm. salol
5	0 00626	Next day

Rockwood (1895) showed, by the method of Siegfried, that normal urine contains both carnic and phosphocarnic acids. He found, as did Siegfried, two compounds in the iron precipitate, one "carniferrin," the iron compound of phosphocarnic acid, soluble in alkalis, and the other a basic iron compound of carnic acid.

Ceconi (1896) states that the organic phosphorus of the urine equals 11-28 mg. per day, the amount varying with the volume; that values greater than 20 mg. are found only in pathological conditions; and that the organic phosphorus of the urine is not affected by variations in the food.

Oertel (1898-9) found, in a study of the urinary phosphorus of 7 healthy men, an average total phosphorus content of 2.0 gm. P_2O_5, and about 0.05 gm. P_2O_5 as organic phosphorus. The highest amount of organic phosphorus for one day was 0.120, and the lowest 0.03 gm. P_2O_5. The amount was not influenced by work, but differed much with individuals.

Keller (1900a) determined that the organic phosphorus of the urine of infants was greater in amount after feeding cow's milk than after feeding human milk, though it was a smaller percentage of the total urinary phosphorus, since the total phosphorus from the cow's milk greatly exceeded that resulting from woman's milk. It varied in amount from less than one to about 10 percent of the total urinary phosphorus.

In a fasting experiment on himself Keller found in a four-day test that the amount increased daily, thus, 0.017, 0.029, 0.034, and 0.057 gm. P_2O_5. These increased amounts constituted increased percentages of the total urinary phosphorus, though this also increased from day to day.

The significance of organic phosphorus of the urine was not established. It did not vary regularly with the phosphorus given in the food, nor with absorbed phosphorus, nor with nitrogen metabolized. It was not influenced by Na_2HPO_4 ingested. On a similar diet normal children excreted more organic phosphorus than did

children suffering from such disturbance as would reduce powers of oxidation. The amount eliminated was not altered by feeding with a very low phosphorus diet.

Lépine (1901) states that in fatty degeneration of the liver its high lecithin content is accompanied by an abnormal glycerophosphoric acid content of the urine, which may reach a value as high as twice the usual amount. He suggests that an abundance of incompletely oxidized phosphorus in urine may be an indication of a fatty condition of the liver.

Mandel and Oertel (1902) observed no change in the organic phosphorus of the urine by food rich in organic phosphorus.

Y. Henderson and Edwards (1903) compared phosphorus figures on the urine by direct titration and after fusion. From the correspondence of results they conclude that no organic phosphorus was present.

K. Bornstein (1905) considered the origin of the organic phosphorus of the urine, in metabolism experiments on himself. Overfeeding with protein did not increase the organic phosphorus of the urine. The author did not determine the source of this organic phosphorus but was of the opinion that it was of endogenous origin.

Symmers (1904-5a, 1904-5b) has investigated the elimination of organic phosphorus in the urine in various pathological conditions. Symmers calls attention to the idea, which has prevailed until recently, that the urinary excretion of organic phosphorus, either in health or in disease, is negligible, and cites 8 earlier investigations of the subject. Symmers states that exercise and diet do not affect the urinary excretion of organic phosphorus. Analyses of the urine of 20 cases, embracing 9 diseases, are given. The organic phosphorus varies from a small part to about nine-tenths of the total phosphorus. Symmers cautions, therefore, against the use of inorganic phosphorus determinations as indices of metabolism. He finds the excretion of organic phosphorus to some extent rhythmical,periods of excessive secretion alternating with what may be either retention or diminished production. Symmers finds organic phosphorus elimination pronounced in lymphatic leukaemia; and also in nervous diseases of degenerative type, to such extent as could not be derived from the destruction of nervous tissue.

In conclusion Symmers says that abnormal increase of organic phosphorus may be explained either as an increase in the production of phosphorized endogenous metabolic products, or as an expression of lessened oxidation, with the organic phosphorus compounds as the end-products.

Symmers determined total phosphorus by titration with uranium nitrate, after fusion; and inorganic phosphate also by uranium nitrate titration, but without fusion. Organic phosphorus was reckoned by difference.

Franchini (1907, 1908a) found glycerophosphoric acid quite variable in amount in the urine of fasting rabbits. When lecithin was fed,the average glycerophosphoric acid content of the urine was increased, but there was no uniform effect noticeable. No choline or formic acid was found as a decomposition product from lecithin.

Plimmer, Dick and Lieb (1909-10) found the inorganic phosphorus of the urine to constitute 90-100 percent of the whole, its amount depending especially on the intake of P_2O_5. Organic phosphorus excretion they found very irregular and not dependent on the diet. They concluded, therefore, that it must be of endogenous origin.

Mathison (1910) determined organic phosphorus in the urine of 5 healthy persons on 3-6 consecutive days, and in the urine of one person as affected by exercise and by the ingestion of glycerophosphoric acid and sodium glycerophosphate. Organic phosphorus was found normally present, usually in amounts greater than 0.1 gm. P_2O_5 per day, though occasionally it fell below this figure, and in one case reached 0.3 gm. The proportion of the total phosphorus present in organic combination varied considerably from day to day but averaged about 6 percent.

The organic phosphorus outgo was not affected by ingestion of glycerophosphoric acid. The organic phosphorus of urine was found readily dialysable and not precipitable by reagents which precipitate protein.

Kondo (1910) studied the effect of organic phosphorus of the food on the organic phosphorus of the urine. With a dog weighing 8 kg. the urinary organic phosphorus varied from 0.0086 to 0.0227 gm. P_2O_5 per day, while the total urinary phosphorus varied from 0.3941-1.6436 gm. P_2O_5 daily. The variations in organic phosphorus, then, were slight in absolute quantity. The proportion of organic to inorganic phosphorus was less (1.2-1.6 percent) on days of excessive phosphorus ingestion, in the shape of brain, casein and thymus, than on intermediate days (2.2-3.5 percent), when the phosphorus was present in horse flesh.

Bogdanow (1911) found the organic phosphorus of the urine to rise significantly immediately after the fall in temperature in croupous pneumonia.

To summarize the evidence: Urine may contain organic phosphorus as glycerophosphoric acid, and as phosphocarnic acid. This fraction is variable in amount from a very small to a large part of the whole, and is too large a factor to ignore in any quantitative work. This organic phosphorus increases after fast (Keller), chloroform anaesthesia, morphine injection, and in many pathological conditions. Its significance is not known. Its amount seems slightly to increase after the ingestion of glycerophosphates, but there is certainly no marked or constant effect of the constituents of the food, either phosphorus-containing or otherwise, or of the amount of phosphorus absorbed, or of the nitrogen metabolism, on this excretion. It appears to be to some extent an individual characteristic, though temporary physiological states seem to be the dominant factors in its quantitative variation.

PHOSPHORUS COMPOUNDS IN THE FECES

The phosphorus compounds of the feces are of mixed origin, being derived in part each from food residues, intestinal excretions, digestive secretions, intestinal epithelium, and bacterial products, the relative proportion of the whole which is contributed by each of these factors varying much with the nature of the diet and kind of animal, the feces being the main vehicle of outgo for metabolized as well as unmetabolized phosphorus in herbivora, while among carnivora and omnivora the main outgo of metabolized phosphorus is through the urine. Since there is no evidence of a direct relationship between food and feces phosphorus compounds, comparatively little attention has been given the determination of the identity of the compounds in the feces. Inorganic salts occur in abundance both as intestinal secretions and as food residues after more or less reapportionment of bases during the digestive process.

The following analyses of the ash of meconium are quoted from F. Müller (1884). Analyses I, II, III and IV are of human meconium and were quoted by Müller from Zweifel.

ASH ANALYSES OF MECONIUM—Percent of Ash

	Horse	Human	I Human	II Human	III Human	IV Human
Insol. in HCl	0.30	0.67	...	...	...	...
Fe_2O_3	0.80	0.87	1.36	2.60	0.86	0.80
CaO	18.76	8.00	31.80	5.70	5.09	9.50
MgO	2.65	4.32	3.60	4.00	7.23	7.92
P_2O_5	10.21	10.66	7.80	5.40	3.20	8.58
SO_3	38.42	47.05	22.30	23.00	39.50	31.90
Alkalis	21.92	24.42	...	K 6.00 Na 24.20	...	Na 15.93 K 7.09
Cl	8.40	...	3.78	2.53	8.68	3.90

Feces from long fasting were shown to resemble meconium. Flesh feces also resemble meconium, and seem to consist largely of excretion products of the intestinal canal rather than of food residues.

Müller also states that the time of passage of the contents of the alimentary tract affects its composition; thus, if the movement be rapid one finds unaltered bile salts and abundant alkali salts, but if the feces remain in the large intestine for a week or more almost no alkali compounds appear in the feces as passed.

Micko (1900), studying feces phosphorus with adult human beings, concludes that the organic phosphorus of the feces does not come for the most part from the food, but that some true nuclein is present in the feces from an ordinary mixed diet and also in the feces from diets of flesh and plasmon.

In a later paper (1900) Micko, Müller, Poda and Prausnitz conclude that human feces are derived in large part, with but few exceptions, from intestinal secretions, and (Müller) that cow's milk used by either infants or adults leaves no phosphorus-rich casein residue in the feces.

Schilling (1901a) states that when the food contains only a small amount of phosphorus the feces contain little or no crystalline tricalcium phosphate.

Von Oefele (1901) states that in diabetes and syncopic neurosis the relative scarcity of triple phosphate crystals in the feces can be explained as due to coexistent phosphaturia. The presence of triple phosphates in the feces was found to have no especial diagnostic value.

A number of workers have determined lecithin in the feces. Among these, Deucher (1898) determined lecithin in the feces in cases of occlusion of the pancreatic duct; P. Müller (1900) found lecithin, calculated as distearyl-lecithin, in milk feces, to the extent of 1.13-10.1 percent of the ether extract, and considered it as derived largely from the food.

Long (1906b) and Johnston (L. & J., 1906, 1907) have studied the phosphorus of the feces fat. Ether-soluble phosphorus compounds which they speak of as lecithins, are found in amounts of from one to several percent, but they suggest that these may be but remotely related to simple distearyl lecithin. They consider that this fraction may come in part each from food, intestinal epithelium, bacteria and bile residues. Commenting on the usual belief that lecithin can not escape digestion, since it is easily split by the pancreatic secretion, they suggest that, while this may be true for the largest part of the food lecithins, it may not be equally true of the lecithins of the bile under certain conditions.

Franchini (1907, 1908a) determined lecithin in the feces of rabbits. There was no uniform increase produced by the feeding of lecithin during fast, but the average lecithin content of the feces was greater.

Peritz (1908-9b) reports lecithin in the feces in cases of tabes and paralysis as varying between 0.1311 and 7.221 gm. per day, there being no evidence of relationship between these amounts and the content of the food in lecithin.

A. Bornstein (1909) found 0.02 gm. lecithin per day in the feces from a diet of crackers and milk.

In connection with a phosphorus metabolism study Rogoziński (1910) made separations of the groups of phosphorus compounds in the feces of a man and of two dogs. The rations and feces phosphorus data were as indicated below.

PHOSPHORUS COMPOUNDS IN HUMAN AND IN DOG FECES

Percent of Total P_2O_5

Period (5 days)	Day	Diet	Lecithin	Phytin	Inorganic	Protein
		SERIES I DOG				
1		Meat, rice, pork fat	1.82	6.34	51.00	40.84
2		Meat, rice, pork fat, phytin	0.45	69.62	14.25	15.68
3		Meat, rice, pork fat	1.46	4.04	47.52	46.98
4		Meat, rice, lecithin	2.19	6.18	48.69	42.94
5		Meat, rice, pork fat	1.20	10.27	39.74	48.79
6		Meat, rice, pork fat, Na phosphate	1.16	8.92	50.43	39.49
7		Meat, rice, pork fat	1.29	6.84	40.15	51.72
		SERIES II DOG				
1		Meat, rice, pork fat	1.68	26.16	42.76	29.40
2		Meat, rice, pork fat, phytin	0.36	62.42	14.71	22.51
3		Meat, rice, pork fat	1.71	18.72	40.68	38.89
4		Meat, rice, lecithin	5.06	13.53	40.21	41.20
5		Meat, rice, pork fat	2.11	20.47	39.94	37.48
6		Meat, rice, pork fat, Na phosphate	1.40	22.84	43.54	32.22
7		Meat, rice, pork fat	1.92	21.61	43.13	33.34
		SERIES III MAN				
1	1	Mixed diet	20.46	3.15	43.82	32.57
	2	Mixed diet	20.18	4.17	46.59	29.06
	3	Mixed diet	18.19	3.01	50.51	28.29
	4	Mixed diet	21.88	0.00	44.87	33.25
	5	Mixed diet	19.49	1.58	44.80	34.13
2	6	Mixed diet, phytin	17.24	2.66	45.67	34.43
	7	Mixed diet, phytin	14.96	2.45	50.77	31.82
	8	Mixed diet, phytin	16.95	1.49	52.88	28.68
	9	Mixed diet, phytin	24.05	0.00	52.87	23.08
	10	Mixed diet, phytin	19.52	0.00	54.38	26.10
3	11	Mixed diet	16.90	0.00	53.97	29.13
	12	Mixed diet	20.45	3.43	50.69	25.43
	13	Mixed diet	21.56	2.24	49.93	26.27
	14	Mixed diet	14.80	0.00	55.47	29.73
	15	Mixed diet	20.47	0.44	47.38	31.71

The group of compounds designated "phytin" is that fraction soluble in acidified water; protein phosphorus is considered to be that portion of the organic phosphorus which is insoluble in acidified water.

In dog feces inorganic and protein phosphorus predominate, though there is also considerable phytin phosphorus, especially when phytin is fed. The feeding of lecithin also increased the feces lecithin.

In human feces there is a very much larger proportion of lecithin phosphorus than in dog feces. The phytin is much more completely absorbed by the human being than by the dog, and the feces phytin is not increased in human beings by the ingestion of phytin. This difference in the utilization of phytin is in harmony with the natural differences of the diets of the two species. The dog has no need for capacity to digest phytin, since there is no phytin in its natural food.

Stutzer (1908) found, in feeding experiments with sheep on hay, that the feces contained metabolic organic phosphorus compounds insoluble in acid gastric juice in quantities greater than would have been expected from the analysis of the food.

Emmett (1909) determined phosphorus on the ether extract of pig feces, and found 0.39-0.74 percent P_2O_5 in this extract.

Lipschütz (1910b) determined that the phosphorus content of the feces of young dogs on mother's milk, cow's milk, meat diet, and phosphorus-poor diet varied between 0.87 percent with mother's milk and 0.60 with meat diet, while the starvation feces contained about the same (0.63 percent) phosphorus content. The phosphorus intake with cow's milk was 0.201 gm. per kg. live weight; with phosphorus-poor diet 0.023-0.031 gm., and on meat diet 0.095 gm., from which it would appear that the phosphorus content of dog feces under these conditions originated, not in the food, but in the secretions of the digestive tract.

Lipschütz quotes figures for the phosphorus content of feces as follows: Blauberg—infants 6-7 days old, 0.26-0.49 percent; Tigerstedt—man on low-phosphorus diet, 0.9 percent; Müller—man, fasting, 1.8-2.2 percent, and dog, grown, fasting, 1.91 percent; and Munk—dog, grown, fasting, 3.65 percent, from which he concludes that the feces arising from the digestive tract of the growing organism is notably poorer in phosphorus than that of adults.

Fraps and Rather (1912) have investigated the composition and digestibility of the ether extract of a variety of hays and fodders, and of certain constituents, among others phosphoric acid, of

the ether extract. Since the ether extract of the feces is to a considerable extent a bile residue, and not directly related to the food, it seems to us that their statements as to the relative digestibility of the lecithin and other constituents of the ether extract are quite without warrant.

VonWendt (1905) and Zuckmayer (1912) both concluded that phosphorus is in the feces largely in the form of the trimetallic phosphates. See p. 184.

Summary. The phosphorus compounds of the feces are not well-known, but have been found to include nuclein phosphorus, inorganic phosphates in a variety of forms, lecithin-like compounds and other organic metabolic products, the nature of which has not been investigated. Studies of the feces in fasting, and during feeding on meat and milk, lead to the belief that a considerable part of the feces phosphorus, especially the lecithin-like compounds, have an origin other than in the food. To relate the feces phosphorus compounds as a whole directly to those of the food, as in computation of digestibility, is without justification.

PHOSPHORUS EXCRETION AS AFFECTED BY ACIDS, SALTS, GENERAL CHARACTER OF DIET, AND SPECIES OF SUBJECT

ACIDS

One of the most potent influences affecting the elimination of phosphates is the ingestion of acids and acid salts. Under this influence calcium and phosphorus, being associated in the body, are affected at the same time, and thus are excreted in combination; increasing acidity of the urine being associated with increased excretion of both calcium and phosphorus.

Schetelig (1880) studied urinary calcium under different conditions with a normal subject and 24 cases of a number of diseases. Incidentally phosphorus was considered. The ingestion of hydrochloric acid caused an increase of both calcium and phosphorus in the urine.

Ott (1886) reported the acid and neutral phosphates of human urine as being in the relation 60:40. He determined that calcium is present in urine in greater amount than the solubility of its acid and neutral phosphates in water would explain, and that the solubility of $CaHPO_4$ is increased by the presence of acid phosphates of the alkalis, gypsum, ammonium chloride and magnesium sulphate. Neutral alkali phosphates decrease the solubility of tricalcio phosphate.

Rüdel (1893a), in experiments on dogs and infants, proved that ingestion of hydrochloric acid, calcium acetate, or chalk, would increase the urinary calcium, while sodium phosphate was without

such effect, and calcium phosphate served markedly to reduce the urinary calcium. Subcutaneous injection of calcium acetate caused increased urinary calcium as also did prolonged peristalsis from *tinct. opii.*

Rüdel (1893b) showed with a nine-months-old infant that the introduction of sodium phosphate into the food would decrease the calcium to 41.76-61.5 percent of the normal. A notable increase in the urinary calcium followed the administration of dilute hydrochloric acid.

In harmony with these observations is that of Gerhardt and Schlesinger (1899) that the administration of sodium bicarbonate markedly reduced the urinary calcium and correspondingly increased the feces calcium. Similarly Proskauer (1910) found an evident increase of calcium and a smaller increase of magnesium in infant's blood in severe digestive disturbance. In harmony with this is the observation of Allers and Bondi (1907) of an increase of calcium in the blood in experimental hydrochloric acid poisoning, from 0.069 gm. to 0.159 gm. in 1000 gm. of blood.

W. Camerer, Jr. (1902b), from a study of conditions affecting ammonia excretion, submits data on the relative amounts of total phosphorus, and phosphorus in acid salts, in the urine, as affected by age, sex, exercise, nature of the food, and the ingestion of acid and alkaline compounds. The figures are as follows:

AVERAGE DAILY TOTAL PHOSPHORUS, AND PHOSPHORUS IN ACID SALTS, IN URINE—Grams

	Grown men on mixed diet	Youths		Children		Men Sp. gr. 1.016	Women Sp. gr. 1.011	Animal food	Mixed diet plus 4-5 gm. H Cl	Mixed diet plus 8 gm. Na HCO
		Resting	Exercise	Sp. gr. 1.0165	Sp. gr. 1.0225					
Total P_2O_5....	2.89	1.80	1.80	0.70	1.08	2.07	1.56	3.5	1.79	2.635
P_2O_5 in acid salts.....	1.70	1.01	0.82	0.38	0.64	1.31	1.14	1.55	1.08	0.70

Here we note a much higher proportion of acid salts resulting from the ingestion of HCl than from $NaHCO_3$.

Folin and Shaffer (1902) found that ingestion of hydrochloric acid increased the outgo of nitrogen, sulphur and phosphorus, without marked change in the proportions between these elements.

VonTabora (1905) studied the phosphorus content of 122 samples of gastric juice from normal and pathological subjects. The phosphorus content of the stomach, with normal or greater acidity, is negligible, following a phosphorus-free test meal, the maximum amounts being about 0.005 gm. P_2O_5 in 10 c.c. of filtered juice. The calcium content was about 0.002 gm. in 100 c.c.

The author concluded that the phosphate content of gastric juice is indirectly proportional to, and dependent on, the degree of acidity, in one and the same individual. In the presence of hydrochloric acid all phosphate was considered to be present in the diacid form; while in anacid conditions the monacid form predominated.

Fitz, Alsberg and Henderson (1907) studied urinary phosphorus elimination in rabbits as affected by the ingestion of hydrochloric acid. The introduction of acid into the circulation increased, in four rabbits, the outgo of phosphorus in the urine. This increase was followed by a decrease, and then after further introduction of acid, by a premortal rise in phosphorus outgo.

This increase in phosphorus elimination, under the influence of acid poisoning, is explained by the conversion of di- to mono-phosphate in the blood, for the neutralization of the acid, and the restoration of the normal proportions of phosphorus in these forms by the elimination of the excess of mono-phosphate.

Granström (1908) found that feeding H_3PO_4 to rabbits increased the feces calcium, and the phosphorus of both urine and feces.

Adler (1909) reports a study of the effects of hydrochloric acid and calcium phosphate administration on the excretion of calcium and phosphorus by human beings, but the brevity of the collection periods renders results of doubtful significance.

Wuertz (1912) found that the addition of HCl to the diet of rabbits did not affect the distribution of phosphorus between urine and feces, the acid being so rapidly absorbed that its ingestion did not increase the length of the acid portion of the alimentary tract, but that the addition of calcium carbonate increased the alkalinity of the intestine, and, therefore, greatly increased the proportion of the phosphorus excreted in the feces.

PHOSPHORUS EXCRETION AS AFFECTED BY SALTS OF SODIUM AND POTASSIUM

Sick (1857) found that the ingestion of sodium phosphate increased urinary phosphorus by more than the added amount, with a decrease of earth phosphates, and increase of alkali phosphates.

C. Ph. Falck (1872) determined, by intravenous injection of sodium phosphate into dogs, that this salt was promptly eliminated by the kidneys, the principal part within a few hours. Doses of 5.4 to 10.2 gm. by intravenous injection (the volume of the solution not stated) caused vomiting.

Bunge (1873) found that potassium phosphate, as well as the citrate and sulphate, has the effect, when ingested by human beings, to cause an increase in the elimination of sodium salts.

Bertram (1878) found that in man potassium citrate decreases urinary excretion of phosphorus but little, while the calcium excretion is greatly diminished. A further decrease of the phosphoric acid takes place if in addition to potassium citrate, calcium carbonate is also given. In herbivora Bertram found that K_2HPO_4 if added to the usual diet led to the appearance of phosphorus in the urine.

P. A. E. Wagner (1892) demonstrated the diuretic effect of disodium phosphate by injecting it in solution into the jugular vein of rabbits. The urine was then collected at 15-minute intervals. The maximum excretion of urine was during the second 15-minute interval.

Gerhardt and Schlesinger (1899) found in diabetes that ingestion of sodium carbonate reduced urinary phosphorus excretion; but this was probably by virtue of its alkalinity alone, and not by virtue of any specific action of sodium, or to the solubility of its compounds.

Desgrez and Guende (1906) studied the influence of phosphoric acid, monosodium phosphate and trisodium phosphate on the metabolism of the guinea pig. Twenty-four male animals were used in four series of six each. The basal ration was consumed *ad libitum*, the amounts consumed being said to be about alike. The only phosphorus metabolism data are figures representing urinary phosphorus outgo. The urinary nitrogen was increased by all of the phosphorus compounds, and in order of their acidity, that is, the neutral phosphate caused the least increase, the acid phosphate the next, and the phosphoric acid the most.

For a computation by Raoult's formula of the molecular weight of the average molecule in the urine in these experiments see Desgrez and Posen (1907).

According to Loewi (see von Noorden, 1907, vol. 3, p. 1079, 1080; German ed. vol. 2, p. 685, 686) von Bunge found that urinary phosphorus excretion is not influenced by sodium salts, but that potassium salts cause a considerable fall in urinary phosphorus. Loewi states that Bertram cleared up the question as to the method of action of potassium in this connection, by the observation (previously mentioned) that the exhibition of potassium citrate (erroneously translated "calcium citrate," Eng. ed.) considerably decreases not only the phosphoric acid but also the calcium in the urine (in one case within three days from 0.5 to 0.28 gram), an action which is not shared by sodium (Beckmann). The cause of the different action of potassium and sodium on calcium excretion in the urine is, according to Loewi, who credits the observation to Bertram, that the calcium phosphates found in the body fluids are insol-

uble in potassium carbonate, and hence can not be excreted in the urine, while they are, however, soluble in the corresponding sodium compounds. Loewi states that the excretion of magnesium is not affected by either potassium (Bertram) or sodium (Beckmann).

Hart, McCollum and Humphrey (1909), in their study of phytin metabolism with a dairy cow, found that the potassium of the feces varies with the phosphorus intake. With high phosphorus intake the potassium is in part deflected from urine to feces, while with a low phosphorus intake the potassium is eliminated mostly in the urine.

Von Hoesslin (1909), in experiments with dogs, studied the effects of sodium chloride, and other salts, on metabolism. He concluded that the addition of sodium chloride to the food increased the outgo of phosphorus, especially in the urine. The excretion of tertiary sodium phosphate by the kidneys is increased by water, and still more by the sodium chloride intake. The phosphorus outgo, especially in the urine, is also increased by overheating. Phosphates added to the diet caused diuresis, and an increase in the percentage content of the urine in phosphorus.

Oeri (1909) studied phosphorus metabolism as affected by ingestion of disodium phosphate. The basal ration was composed of normal foods in usual combinations. The subjects of the experiments were a woman, aged 35 years, weight 55 kg., and the author himself, aged 25 years, weight 93 kg. The numerical data follow.

AVERAGE DAILY PHOSPHORUS BALANCES OF MATURE MAN AND WOMAN AS AFFECTED BY INGESTION OF DISODIUM PHOSPHATE—Grams

Periods and days	Intake P_2O_5	Urine P_2O_5	Feces P_2O_5	Total excreted P_2O_5	Urine, percent P_2O_5	Feces, percent P_2O_5	Balance P_2O_5	Diet
Fore-period 1-6	5.45	2.24	2.50	4.74	47.3	52.7	+0.71	Milk, veal, bouillon, bread, potatoes, apples, sago, butter, coffee, jelly.
Phosphate fed 7	7.48	2.62	3.90	6.52	40.2	59.8	+0.96	Same plus disodium phosphate.
After-period 8-12	5.45	2.02	3.07	5.09	39.7	61.3	+0.36	Same without phosphate.
Phosphate fed 13	7.48	2.64	3.62	6.26	42.2	57.8	+1.22	Same with phosphate.
After-period 14	5.45	2.15	2.83	5.98	52.7	47.3	−0.53	Same without phosphate.
Fore-period 1-9	6.54	3.62	3.31	6.93	52.3	47.7	−0.39	Milk, veal, bouillon, bread, potatoes apples, pea soup, butter, coffee, beer, jelly.
Phosphate fed 10	8.57	3.64	4.06	7.70	47.0	53.0	+0.87	Same plus disodium phosphate.
After-period 11-17	6.54	3.39	3.10	6.49	52.3	47.7	+0.06	Same without phosphate.

The sodium phosphate was without marked or consistent effect on the partition of phosphorus between urine and feces.

EFFECTS OF CALCIUM AND MAGNESIUM ON PHOSPHORUS ELIMINATION

Calcium Carbonate. Riesell (1868) found that the ingestion (by himself) of large amounts of calcium carbonate (10 gm. with each meal and some with the drink) decreased the urinary phosphorus to about one-half the normal, but during four days of such chalk treatment the urinary phosphorus rose nearly to the normal, apparently through the absorption of the calcium phosphate formed in the intestine. Under the influence of the chalk, the alkali phosphates of the urine were largely replaced by alkaline earth phosphates.

Schetelig (1880) did not observe a decrease of urinary phosphorus from taking calcium carbonate for 2 days in 3-gram doses. The amount was perhaps insufficient.

E. Lehmann (1882, 1894) determined that the alkaline-earth carbonates, when ingested, have the effect quantitatively to reduce the urinary phosphorus.

Rüdel (1893a) shows that the administration of calcium carbonate may cause some increase in the urinary calcium of children, but not by any means in proportion to the intake.

Strauss (1896) studied the effect of calcium carbonate ingestion on the elimination of phosphorus, uric acid and purin bases in man. Ingestion of calcium carbonate caused a decrease in urinary phosphorus, which did not disappear immediately after the withdrawal of the carbonate from the food, but only after about three days. The decrease in urinary phosphorus is due to decrease principally in the amount of monosodium phosphate, but partially to decrease in disodium phosphate, thus decreasing the urinary acidity but never causing alkalinity. Uric acid and purin bases were not affected. Urinary calcium was slightly increased.

Herxheimer (1897) tested the effects of ingestion of calcium carbonate baked into bread in the amount of 5 percent of the same. The carbonate had the effect to decrease the urinary phosphorus quite markedly, and also to increase the feces phosphorus, though to a less extent, the calcium apparently increasing the retention of phosphorus, though phosphorus in the food was not determined. There was in the urine a greater reduction of monophosphate than of diphosphate, which produced in the latter a great relative increase. Herxheimer states that 18 grams of carbonate baked in the bread was more effective than 30 grams as a powder.

Volhard (1904) found that great quantities of calcium carbonate in the food did not seriously affect digestion or phosphorus metabolism.

G. Zuelzer (1905) states that calcium affects the urinary phosphorus by uniting with this element in the intestine and passing off in this form in the feces. With a lime-poor diet the feces are poor and the urine is rich in phosphorus.

On the basis of work by Zerner and Ritter, and others, vonNoorden and Dapper (vonNoorden 1907, III, 946) state that even after the ingestion of considerable quantities of calcium carbonate the urine remains slightly acid, since the calcium is excreted almost entirely by way of the intestine, in which it combines with phosphoric acid, thus restricting its absorption. Thus the total phosphorus of the urine is decreased, and, as the reaction of the urine approaches alkalinity, the proportion of disodium to monosodium phosphates is modified in favor of the former. This decrease of phosphates involves an absolute and a relative decrease of monosodium phosphate, a substance which directly promotes the precipitation of uric acid; while the relative excess of disodium phosphate, which is capable of dissolving uric acid, is left free to exert a greater effect.

Kochmann and Petsch (1911) found, in metabolism experiments with dogs, that increasing the lime of the diet, the phosphorus remaining constant, increased the feces phosphorus and decreased the urine phosphorus. When a calcium equilibrium had been established and protein, carbohydrates and fat were added to the ration, the calcium intake remaining constant, the calcium equilibrium was disturbed, and lime was lost from the bones.

Bertram (1878) and Renvall (1904) also found that calcium carbonate in the diet served to deflect phosphorus from urine to feces.

Various Salts of Calcium and Magnesium. Tereg and Arnold (1883) reported results of experiments with dogs in which they compared the effects on metabolism of the ingestion of calcium carbonate and primary, secondary and tertiary phosphates as supplements to uniform basal rations.

The authors interpret the negative nitrogen balance in the fourth period as being due to the influence of the primary calcium phosphate in causing increased katabolism of body protein, and cite in support of this idea the coincident loss of calcium and phosphorus.

We would suggest that, comparing the calcium and phosphorus balances of Periods II, III and IV, the smaller the proportion of calcium to phosphorus in the salt supplement the less is the storage, or the greater the loss, of both calcium and phosphorus, suggesting that in these rations the lack of proportion between these constit-

uents restricts the usefulness of both. The great increase of phosphorus retention caused by the ingestion of lime in the fifth period shows that in these rations the lime content limited the deposition of phosphorus.

AVERAGE DAILY NITROGEN, CALCIUM AND PHOSPHORUS BALANCES WITH A DOG ON NORMAL RATIONS SUPPLEMENTED BY INORGANIC SALTS—Grams

Period and date	Body weight, initial and final	N Food Urine Feces Balance	CaO Food Urine Feces Balance	P_2O_5 Food Urine Feces Balance	P_2O_5: N in urine	Rations
I	32000	22.68 17.76 4.31	0.780 0.0455 1.465	5.040 3.087 3.003		600 gm. dog biscuit
Nov. 12-15	32900	+0.61	−0.7305	−1.049	17:100	
II		22.68 17.45 4.90	5.140 0.1077 4.960	8.710 3.539 4.728		600 gm. dog biscuit; 10 gm. $Ca_3(PO_4)_2$
Nov. 18-21	constant	+0.33	+0.0701	+0.443	17:100	
III		22.68 17.30 5.10	4.688 0.053 4.557	9.350 4.496 4.810		600 gm. dog biscuit; 10 gm. $CaHPO_4$
Nov. 29-Dec. 2	constant	+0.28	+0.078	+0.044	32:100	
IV	32900	22.68 18.75 4.83	1.905 0.0779 1.860	9.255 5.895 3.853		600 gm. dog biscuit; 7.5 gm. $CaH_4(PO_4)_2$
Dec. 5-12	32600	−0.90	−0.0354	−0.493	31:100	
V		22.68	6.380 0.158 4.310	5.040 1.336 2.088		600 gm. dog biscuit; 10 gm. chalk
Dec. 19-22		.....	+1.914	+1.616		
VI	33500	22.58 16.45 3.90	0.144 0.020 0.100	2.802 2.532 0.237		600 gm. horse flesh; 100 gm. horse fat
Dec. 28-31	33520	+0.19	+0.022	+0.033	19:100	
VII	33520	22.58	4.052 0.029	7.112 3.402		600 gm. horse flesh; 100 gm. horse fat; 10 gm. $CaHPO_4$
Jan. 7-10	33520	.....	.....	.....		
VIII	33520	22.58	0.894 0.061 0.740	5 612 4.572 0.909		600 gm. horse flesh; 100 gm. horse fat; 5 gm. $CaH_4(PO_4)_2$
Jan. 13-16	33430	.....	+0.093	+0.131		

Tereg and Arnold compute that in Period IV the phosphorus loss could not all be accounted for as coming from the loss in flesh, a portion apparently coming from the bones. That all three of these phosphates were absorbed is not to be questioned, though the authors note that the calcium and phosphorus apparently absorbed, that is, missing from the feces, are not in proportional amounts. Either these salts were decomposed in the intestine, and

the parts absorbed independently of each other, or, after absorption, they were decomposed in the blood, and the parts eliminated in unlike portions through the intestines and the kidneys.

Of the primary salt (Period IV) nearly twice as much calcium and phosphorus were eliminated in the urine as of the secondary salt. In periods VI, VII and VIII where the basal ration was meat, the primary salt caused a much greater increase of the calcium and phosphorus of the urine than did the secondary salt, and in injection experiments the authors noted similar increase of the calcium and phosphorus of the urine. It is their opinion therefore that the primary salt is absorbed as such from the intestine.

Steel and Gies (1907a) determined the effects of the addition of bone ash to a diet of prepared meat, cracker meal, lard and water, on the urinary excretion of calcium and phosphorus by dogs. It was desired to use bone ash in the ration to give bulk and body to the feces.

Bone ash seems not to alter the urinary elimination of calcium, but a decrease of urinary phosphorus from 0.460 to 0.244 gm. P_2O_5 in 21 days, during the feeding of bone ash, shows that the use of bone ash for the purpose intended would be justifiable only in such experimental work as would be unaffected by a decrease of phosphorus absorption or change in path of outgo.

Lothrop (1909) investigated the effect of bone ash in the diet on the metabolism of the dog. The ingestion of bone ash decreased the urinary phosphorus.

Hart, McCollum and Humphrey (1909) found, in their study of phytin metabolism with a milch cow, that calcium, magnesium and phosphorus were excreted principally in the feces, and that a low phosphorus intake served to increase the urinary elimination of calcium.

R. Berg (1910a) conducted balance experiments on himself, using a basal ration to which he added, in different periods, various organic and inorganic phosphorus compounds. Tricalcic phosphate he found excreted largely as such in the feces. The dicalcic phosphate was excreted in part as tricalcic phosphate and magnesium ammonium phosphate. Hypophosphites were almost all excreted unchanged. Berg considers that the best source of calcium is green vegetables prepared so as to retain their salts.

De Jager (1910) submits the following data showing the effects of calcium salts on urinary phosphorus in man.

URINARY PHOSPHORUS AS AFFECTED BY CALCIUM SALTS—Grams

Days	Periods	Ave. Daily P_2O_5
4	Preliminary	2.462
10	4 gm. Ca-sulphate daily	2.344
16	Interval	2.489
5	7.5 gm. Ca-lactate daily	2.087
18	Interval	2.199
10	6 gm. Ca-sulphate daily	1.767
14	After period	1.999

The slight decrease of urinary phosphorus produced by the calcium sulphate is doubtless due to the relative insolubility of this salt. The lactate, with its weak, oxidizable acid radical, yields much more of its calcium free for combination and excretion with phosphorus in the feces.

A. R. Rose (1912a), in his phytin metabolism study with a cow, found that the ingestion of calcium and phosphorus as the phytate deflected a part of both the calcium and magnesium from urine to feces, the calcium added as the phytate also being eliminated by the feces. With decreasing phosphorus in the food there was an increase of urinary calcium.

Gregersen (1911) showed with rats that calcium and magnesium tend to deflect phosphorus excretion into the feces, either when the phosphorus excreted is contained in the food, or when it is metabolized phosphorus from the body. Gregersen also found that this effect was not affected by such acid-saturating salts as sodium bicarbonate.

In experiments with swine, Forbes, Beegle, Fritz and Mensching (1914) found that in common foods magnesium tends to deflect the phosphorus excretion from urine to feces, and excessive phosphorus content of the ration seems to limit the absorption of magnesium. With an average daily intake of 2.17 gm. magnesium and 5.40 gm. phosphorus there was storage of magnesium, but with an intake of 9.28 gm. magnesium and 20.71 gm. phosphorus there was loss of magnesium, apparently combined with phosphorus, through the feces.

EFFECTS OF DIET AND SPECIES ON PHOSPHORUS ELIMINATION

The bearing of species, especially as determining prevailing diet, on the paths of elimination of phosphorus is marked. The herbivora normally consume a diet which is comparatively poor in phosphorus and rich in alkalis and alkaline earths. The omnivora and carnivora, on the other hand, live on a diet which is so much richer in phosphorus and poorer in mineral bases that a different and much more extensive acid-neutralizing capacity has been

evolved. Thus, the herbivora excrete their mineral acids in combination with fixed alkalis, while the omnivora and carnivora are able to excrete the same largely combined with ammonia. During the suckling period, however, the excretion of phosphates is much the same in both classes of animals. A few of the many papers showing the different methods of elimination of phosphorus in herbivora and other animals are mentioned in brief.

Bischoff (1867) found that in dogs phosphorus is excreted to the extent of about 12-thirteenths in the urine, mostly combined with the alkalis, while the remainder leaves the body in the feces combined principally with calcium, iron and magnesium.

Bertram (1878) concluded that the absence of phosphorus from the urine of herbivora was due to the richness of the food in vegetable alkali compounds and calcium salts, alkaline liquids containing carbonates having no solvent power for calcium phosphate, though they do dissolve magnesium phosphate.

F. Müller (1884) concluded from analyses of meconium and of feces from diets of meat that the dog excretes its lime mostly through the feces, while magnesium, and to a greater extent still, phosphorus, is excreted chiefly through the urine. The content of the feces in the alkalis varies indirectly with the length of stay in the intestine.

Weiske (1872b) analyzed the urine of two goats, one receiving milk alone, *ad libitum*, and the other green clover and turnip leaves. The ash analyses are as follows:

	Vegetable diet	Milk diet
K_2O	34.91	42.83
Na_2O	22.48	14.05
CaO	0.77	0.98
MgO	3.28	0.61
Fe_2O_3	trace	trace
CO_2	10.40	none
SiO_2	0.59	none
SO_3	16.89	3.02
P_2O_5	trace	22.22
Cl	13.35	20.67
	102.67	104.38
O out for Cl	3.01	4.66
	99.67	99.72

On a milk diet the goat excretes much phosphorus in the urine; on this vegetable diet no phosphorus was excreted in the urine.

Jordan (1885-6) found in the urine of a sheep nearly half of the total potassium outgo, but no phosphorus.

E. Wolff (1886) reports determinations of the phosphorus of clover hay, and of the feces resulting from its being fed to horses. The feces phosphorus equalled the food phosphorus. With a ration of oats, straw and meadow hay the feces phosphorus was 98.9 percent of the food phosphorus.

Grundzach (1892) determined the ash constituents of normal human feces, and found in the ash 29.25 percent CaO and 13.76 percent P_2O_5.

Paton, Dunlop and Aitchison (1899-1900) made a general study of the paths of elimination of phosphorus compounds by animals, and their principal findings are as follows:

In dogs, on a vegetable diet, a large proportion of the phosphorus of the food is not excreted in the urine.

In dogs, on a diet of dog's biscuit and milk, a large proportion of the phosphorus injected subcutaneously as sodium phosphate is not excreted in the urine (no food or feces data).

During lactation there is a diminished urinary excretion of phosphorus by the dog, and a diminished feces excretion of phosphorus by the goat.

In the goat none of the phosphoric acid injected subcutaneously as sodium phosphate, or formed in the body, or contained in the food, is excreted in the urine.

The administration of calcium glycerophosphate by the mouth causes no increased excretion of phosphorus in the urine of the dog, or in the urine or milk of the goat.

Rumpf and Schumm (1900) made urinary phosphorus estimations in a human metabolism experiment with a vegetable diet. The subject, weighing 62.5 kg. at the beginning of the 8-day experiment, gained 1.7 kg. during this time on a ration supplying 3431 calories and 73.88 gm. protein daily. The urinary nitrogen was 6.91 gm., and urinary phosphorus (P_2O_5) 1.38-2.43 gm. per day.

Bergmann (1901) studied phosphorus elimination in the dog and the sheep. Sodium phosphate injected subcutaneously into a dog receiving a ration of meat and bread was eliminated in the urine. The same result was obtained when, in addition to the phosphate injection, calcium carbonate was added to the diet.

With a wether, on a diet of hay and oats, sodium phosphate was injected subcutaneously, and all of it was excreted by the intestine, the urinary phosphorus remaining unweighable.

Glycerophosphoric acid, likewise, when subcutaneously injected, was excreted by the dog in the urine, and by the wether in the feces, as inorganic phosphoric acid. Bergmann also notes the well-known fact that, while dogs normally excrete P mostly in the urine, if Ca is abundant in the food much P is excreted with it in the feces.

Tangl (1901) found in metabolism experiments with horses, on hay and oats, that more than half of the calcium, about three-fourths of the magnesium, and nearly all of the phosphorus of the

food is eliminated in the feces. Tangl concluded that a horse was able to obtain its calcium needs from the same low-calcium fodder which with cattle may produce malnutrition of the bones. See also W. Camerer, Sr. (1904); composition of human urine as affected by animal and vegetable diet, disease, etc.

Gouin and Andouard (1907) conducted experiments showing that a calf receiving milk alone excreted 83.33 percent of the food phosphorus in the urine. An addition of powdered bone to the food did not alter the percent of the total phosphorus excreted in the urine.

Another calf received 55.6 gm. P_2O_5 in milk and vegetable foods, and excreted 13.74 percent of this amount in the urine; when 29.22 gm. more P_2O_5 was added in the form of powdered bone the amount of phosphoric acid in the urine was increased by 2.36 gm., and the percent of the total phosphoric acid of the food found in the urine was reduced to 11.79.

A third calf received no milk in the food. The urine contained 1.15 gm. phosphoric acid, which was 7.85 percent of the total excretion. When 33.5 gm. P_2O_5 was added to the diet in the form of bone, the quantity in the urine increased to 6.35 gm., and the percent of the total excretion to 20.92.

Another calf passed no phosphorus in the urine. Powdered bone was added to the diet in the amount of 18.31 gm. daily for 7 weeks. The storage of phosphoric acid was 17.5 gm. per kilogram of increase in live weight.

These data show that bone phosphate may be retained by calves, and that the vegetable foods used tended to deflect the excretion of the absorbed phosphorus of the bone meal from urine to feces. The authors (G. and A.) referred these results to differences in digestibility of the phosphorus in the different forms.

Magnus-Levy (vonNoorden 1907, I, p. 41) speaks as follows regarding the effects of species and diet on phosphate elimination:

"The complete removal of the phosphoric acid from the urine of man and of dogs, as in the case of herbivora, cannot be effected. Acid sodium phosphate, when subcutaneously injected into sheep, is excreted in the feces, and in dogs appears almost entirely in the urine, even when the intestine is overladen with calcium salts (Bergmann).

"In dogs the separation of phosphoric acid by the kidneys is not affected by the addition of alkali if the food is not rich in calcium (Beckmann); the phosphoric acid salts of the sodium and calcium of the food then pass out almost entirely by way of

the kidneys (Markuse, Leipziger, Zadik). It is only when an excess of calcium and alkali are together present in the food that the phosphoric acid usually excreted by the kidneys is conducted from and to the intestine."

Gouin and Andouard (1908) attempted to answer the question as to why adult cattle do not secrete phosphorus in the urine. In the light of current understanding, however, their conclusions as to kidney resistance to phosphates are no longer significant.

Oeri (1909) found that with mature human beings the excretion of calcium and phosphorus by the intestine is increased (1) by diets, which, like milk, contain considerable inorganic phosphorus and calcium, (2) by a diet rich in phosphorus, when calcium is separately administered, and (3) by a calcium-rich diet, when inorganic phosphorus is superposed, that is, whenever phosphorus and calcium are associated within the body.

Stutzer (1910) submits analyses of the urine and feces of the common farm animals, showing the content of mineral elements in these excreta. The cows used were animals giving 12-15 liters of milk on medium rations of green and dry fodder. The sheep received hay only. To the pigs were fed potatoes with green fodder, but no milk. The specific gravity of the urine was as follows: Sheep 1.038; horse, 1.035; cow, 1.037; pigs, 1.020. There was much similarity in the methods of elimination of the several mineral elements by these animals. The influence of species on the paths of excretion could only be determined by feeding the animals to be compared all on the same ration.

ANALYSES OF FRESH URINE AND FECES—Parts per 1000

	Urine				Feces			
	Sheep	Horse	Cow	Pig	Sheep	Horse	Cow	Pig
Water	903	926	923	966	680	750	835	800
Organic material	70	47	57	23	295	230	150	160
Nitrogen								
(a) Total amount	15.8	15.2	15.0	6.4	6.2	5.6	5.9	6.0
(b) Easily soluble	15.8	15.2	15.0	6.4	0.5	0.5	0.6	0.8
Phosphoric acid								
(a) Total amount	1.3	0.05	1.5	1.6	3.0	3.0	2.8	6.0
(b) Easily soluble	1.3	0.05	1.5	1.6				0.5
Potassuim	18.5	16 5	15.5	8 0	1.7	3.3	1.4	5.0
Calcium	1.8	3.2	0.3	0.1	4.0	2.3	2.4	0.5
Magnesium	2.5	2.4	0.1	0.8	2.4	1.0	1.8	0.2
Sulphuric acid	1.0	1.6	0.3	2.7	1.4	0.5	1.2	0.6
Chlorine	3.8	3.0	1.0	1.0	1.0	0.1	0.1	0.1

Summary. The ingestion of acids or acid salts, or acid-formation in the body, increases urinary calcium and phosphorus, and increases the proportion of acid phosphates to total phosphates in the urine.

The alkaline earths decrease urinary phosphorus elimination by uniting with phosphorus in the intestine to form difficultly soluble salts, thus hindering phosphorus absorption.

Calcium carbonate causes a considerable replacement of alkali phosphates by alkaline earth phosphates in the urine. The decrease of alkali phosphates is more largely mono- than di-sodium phosphate.

Sodium phosphate is promptly eliminated by the kidneys and has a diuretic effect. Sodium chloride also has some tendency to increase the urinary phosphorus. Sodium carbonate may reduce urinary phosphorus excretion when this is due in part to acidosis.

Potassium phosphate, as well as other potassium salts, increases the excretion of sodium salts. Potassium phosphate added to the usual diet of herbivora, leads to the appearance of phosphorus in the urine. In man, potassium citrate causes a fall of calcium phosphate in the urine by virtue of the insolubility of calcium phosphates in potassium carbonate. Sodium salts have not this effect.

Calcium phosphates affect phosphorus outgo in the urine in accord with their acidity; the more acid the salt, the greater is the urinary excretion of calcium and phosphorus. The ingestion of bone ash decreases urinary phosphorus, probably through hindering phosphorus absorption.

Calcium lactate, like the carbonate, may decrease urinary phosphorus. Calcium sulphate appears to decrease urinary phosphorus to a very slight degree.

The phosphorus of the diet of carnivora is eliminated principally in combination with alkalis in the urine. The remainder is eliminated in combination with iron, magnesium and calcium in the feces. Carnivora excrete their magnesium more largely than their calcium in the urine.

Sodium phosphate, injected subcutaneously in the dog, is excreted in the urine even if calcium carbonate be added in quantity to the food.

Calcium added to the food of carnivora increases the feces phosphorus; and on a vegetable diet carnivora excrete a large part of the phosphorus in the feces.

Herbivora, in accord with the high calcium content of the diet, excrete almost all of their phosphorus in the feces, the urine usually being practically free from phosphorus. Subcutaneous injections of sodium phosphate are excreted in the feces.

During starvation, or on an animal diet, such for instance as milk, herbivora excrete much calcium and phosphorus in the urine.

During lactation there is, with carnivora, a decrease of urinary phosphorus; with herbivora there is a decrease of feces phosphorus.

Human beings excrete their phosphorus according to the same laws as carnivora and herbivora, the path of outgo varying with the diet. The prevalence of meat and cereals, which have acid ash, in ordinary mixed diets, deflects the larger part of the phosphorus into the urine. Vegetable diet or calcium carbonate increases the feces phosphorus, but the complete deflection of phosphorus from the urine to the feces has not been accomplished.

On a milk diet three-fourths of the phosphorus is excreted in the urine by infants, and nearly the whole of it by calves.

The alkaline earths deflect metabolic phosphorus as well as food phosphorus into the feces, and fasting feces contain considerable amounts of calcium and magnesium phosphate.

The balance of magnesium may be changed from positive to negative in swine by excessive ingestion of phosphorus in common foods, the loss occurring through the feces.

RELATIVE METABOLISM OF PHOSPHORUS AND OTHER ELEMENTS

There is, without doubt, a certain interdependence of all of the constituents of the body, in their metabolism; for instance, if nitrogen is lacking in the ration the metabolism of all other elements which are used with nitrogen will be affected in some measure, the degree depending on the extent and duration of the nitrogen deficiency.

The less the available supply of any nutrient, compared with the demand for the same, the more definitely does it become the limiting factor in production, and the more closely does its metabolism measure that of the body as a whole. Any element, therefore, might become the limiting factor in metabolism; thus, on a ration which is practically iron-free, the total growth might vary directly with the iron content of the ration.

In view of their distribution and relationships in the tissues it might be supposed that nitrogen, sulphur, calcium and phosphorus would ordinarily be found somewhat closely interdependent in metabolism; and since phosphorus, as a universal cell constituent, is concerned in all growth and production, it would be assumed that this element would be found quantitatively related especially to those other elements whose metabolism is dominant during the particular kind of growth or production under observation; thus for the maintenance and repair of the mature animal, nutrients are used in

certain rather definite proportions, one to another; during normal growth the proportions would be somewhat different, and it is quite conceivable that pregnancy, lactation, egg-laying and wool-growing should each have some special requirements for nutrients which would affect their relative quantitative metabolism; further, conditions may be favorable for the growth of bone, without providing liberally for other increase. In each of these phases of normal metabolism phosphorus is involved, and its quantitative relations to other elements have been the subject of study and record, the object being, ordinarily, the determination of the states and conditions of nutrition as made manifest by the quantitative and qualitative estimation of the constituents which have been concerned. A method of frequent use is, for instance, the estimation of relative metabolism of bone and soft parts by the relation of the details of the income and outgo to the composition of these tissues.

We have as the several factors of such considerations first, two possible sources of the constituents involved; the nutrients of the food, and products of tissue katabolism; second, two possible methods of disposition of these constituents, namely, retention and outgo. Usually our observations are confined to the determination of final or net balance, the relative amounts of the constituents retained or lost indicating the identity of the parts involved.

Some limitations of the value of this method of study are that we do not know that all organs are katabolized *en masse*, nor that this process is not to any extent partial or selective; and further, we know very little of the resynthesis of katabolized nutrients. Participation of products of tissue katabolism in synthetic or retention processes may sometimes be inferred from the outgo of accompanying products which are not retained; thus purin nitrogen elimination may signify the katabolism of nucleins under circumstances where the subsequent retention of the accompanying phosphorus and non-purin nitrogen would mask this process.

In spite of the uncertainties attending these attempts to judge of the origin of katabolized nutrients from the composition of the excreta, the method has its uses, though in times past it has been overworked.

The supplementary capacities of the intestine as a means of elimination of katabolized constituents require that the feces as well as the urine be involved in such studies. Conclusions resting on urine analyses alone must be considered as open to question.

Bischoff (1867) concluded that nitrogen and phosphorus excretion rise and fall together, except in fasting; the phosphorus excretion then being relatively greater, the increase being due,

according to Bischoff, to a loss of phosphates from the plasma, without corresponding protein metabolism. This extra phosphorus outgo in fast is now often ascribed to bone katabolism.

J. Forster (1873b) published urinary nitrogen and phosphorus data from a man on a meat diet which show, in considerable measure, at least a temporary independence of nitrogen and phosphorus metabolism. The figures are given below.

EXCRETION OF NITROGEN AND PHOSPHORUS IN THE URINE OF A HEALTHY ADULT ON A MEAT DIET DURING TWENTY-FOUR HOURS—Grams

Hours during the day	N	P_2O_5
10 A. M.—1 P. M.	2.74	0.76
2 P. M.—5 P. M.	3.51	0.62
6 P. M.—9 P. M.	3.36	0.42
10 P. M.—1 A. M.	3.36	0.41
2 A. M.—5 A. M.	2.52	0.32
6 A. M.—9 A. M.	2.56	0.29

A healthy adult ingested at 9 A. M. 500 gm. of finely chopped flesh, containing 18.04 gm. N and 48.3 gm. fat, after having fasted since the preceding noonday meal. He then drank water but took no other food for 24 hours. During this time he excreted nitrogen just about equal to the total present in the 500 grams of meat; and of phosphorus, we compute, 3 times as much as was in the meat. These facts, taken in connection with the rates of excretion as shown by the above figures, exhibit the truth that there is no close relation between urinary nitrogen and phosphorus excretion. The large phosphorus excretion and the steady decline in the rate of elimination show the influence of the previous diet.

W. Zuelzer (1876) published extensive papers on the proportions of nitrogen and phosphorus in the urine of human beings and of dogs in various states of nutrition. In the absence of food and feces data the significance of the conclusions is limited, but certain notes of interest are recorded.

With a dog, the P_2O_5 of the urine from a fat-free flesh diet was 12.8 percent, during fast 8.7 percent, while receiving potatoes 27.1 percent, and while receiving rye bread 25.3 percent of the amount of the nitrogen.

The chief meal of the day exerts an influence on the nitrogen and phosphorus of the urine of the hours immediately following, while this influence diminishes with lapse of time thereafter.

In a table of ratios of phosphorus to nitrogen in the urine at different ages, from infancy to old age, it is shown that the proportion of phosphorus to nitrogen is greatest in infancy, and decreases

rapidly during the period of growth. There appears to be little change during the middle years of life, but there is evidence of a slight increase of phosphorus in proportion to nitrogen in old age. These figures must depend largely on the prevailing diet at the various ages. Zuelzer was of the opinion that increased phosphorus excretion signified loss from the nervous system, an idea now long since abandoned.

C. Voit (1881) submitted the following figures for the proportions of nitrogen and phosphorus in dog urine under different conditions:

$N:P_2O_5$ on meat diet	8.1:1 Bischoff
$N:P_2O_5$ during fast	6.4:1
$N:P_2O_5$, diet of N-poor bread	3.8:1

Feder (1881) attempted to determine a normal ratio of P, S and N in the urine during fast, and feeding on various diets. This he found it impossible to do. He also showed that the hourly variations in the phosphorus outgo, and in the proportion of nitrogen to phosphorus in the outgo, could not be due directly to nerve katabolism, a fact which becomes obvious when we consider the amounts of these variations in connection with the phosphorus content of the nervous system.

W. Zuelzer (1881a) determined the proportion of $N:P_2O_5$ in the muscular system as 100:15, in nerve substance as 100: 45 and in blood as 100:4. He made much of the idea (1881b) of determining the source of the nitrogen and phosphorus of the urine by their proportionate amounts, but ignored the feces. Zuelzer (1881a) stated that a large relative amount of phosphorus as compared with nitrogen in the urine, or a high content of glycerophosphoric acid, indicates nerve katabolism.

Politis (1884) considered the proportions of nitrogen and phosphorus in the urine of dogs receiving brain in the food, and also the hourly variation, during two days, of the nitrogen and phosphorus of the urine. He reached the conclusion that urinary nitrogen and phosphorus data alone were insufficient to demonstrate the breaking down of brain substance. The hourly curves for nitrogen and phosphorus elimination during the feeding of brain were much the same.

Kolpakcha (1888) studied the source of the nitrogen of the urine in 8 extensive balance experiments with dogs, by comparison of the relative amounts of the various constituents of the food with the relative amounts of these same constituents in the tissues of the animal, and in the excreta. The author gives formulae for determining mathematically the proportion of food-, circulating- and tissue-protein katabolized.

Among the conclusions reached by the author are the following: In fasting, two kinds of protein are broken down, (1) "stored protein," or protein stored in the body, after excessive feeding, that has not had time to become part of the tissue protein, and (2) tissue protein, or protein that is really a part of the tissue of the body. The former is said to be broken down with comparative ease, the latter being rather stable. From the ratio of phosphoric acid to nitrogen in the urine it is considered that the cleavage of tissue protein begins on the first day of fasting, though it is stored protein especially which is broken down. As the stored protein is exhausted the organism approaches a condition in which it must live entirely on its own tissues. The author believes that the increased amount of phosphoric acid observed in the urine after a fast of considerable duration, or when the animal is receiving an insufficient amount of food, is due to autolysis of the bones, since there is during these conditions an increase in the proportion of alkaline earth phosphates to alkali phosphates in the urine. He also believes, in harmony with Forster's conclusions, that when the organism is supplied with food poor in phosphoric acid it retains some of the phosphoric acid from the protein which is broken up.

Von Tschirwinski (1889) studied the relative development of the bones and teeth of sheep, and found results not in harmony with the theory of an interdependence between the time of cutting teeth and the development of the bones.

Bergell (1898b) states that normal storage of nitrogen and phosphorus is marked by a relation of one to the other like that in muscle.

Von Moraczewsky (1901) showed that, in a 6-day balance period, with a case of acromegaly, the phosphorus retention was double the amount of the calcium retention. A 6-day period, however, is insufficient for reliable conclusions as to mineral metabolism.

Sivén (1901) notes the lack of parallelism between nitrogen and phosphorus metabolism, which fact he relates to the difference of origin of these constituents, since the outgoing phosphorus is derived in part each from organic and inorganic phosphorus compounds in the body.

Dapper (1902) investigated the question as to the method of retention of nitrogen in a man 26 years old. Data from this work are below. In periods II and III the ratios of $N:P_2O_5$ in the amounts retained were 1.69:1 and 1.24 :1, respectively, while the ratio in muscles is 7.6:1. The considerable amounts of calcium and phosphorus retained must have been deposited largely in the bones.

AVERAGE DAILY NITROGEN, CALCIUM AND PHOSPHORUS BALANCES WITH A MAN TWENTY-SIX YEARS OLD—Grams

Periods	Intake			Excreta			Balances		
	N	P_2O_5	CaO	N	P_2O_5	CaO	N	P_2O_5	CaO
I 6 days....	20.247	5.111	3.547	18.07	5.617	4.237	+2.18	—0.409	—0.690
II 12 days....	20.093	7.033	4.818	16.774	5.022	3.465	+3.32	+1.961	+1.354
III 9 days....	24.581	7.806	4.891	22.093	5.746	4.375	+2.55	+2.059	+0.495

In balance experiments by Tangl (1902a, 1902b) with horses (see Phos. Req. of Horses) we see a case of deficiency of phosphorus in a ration limiting calcium retention, the calcium not being retained in proportion to absorption. On the hay ration the phosphorus was insufficient, while there was considerable calcium retention. In the oats and hay ration, with a reduced calcium intake, there was an increased calcium storage, because of the presence in this ration of phosphorus sufficient to cause retention and allow of the deposition of calcium phosphate in the bones.

Gilbert and Posternak (1903) submitted figures showing that the proportion of nitrogen to phosphorus in the urine is so variable that we must consider the phosphorus requirement as in large measure independent of that for nitrogen.

Ehrström (1903a), (see Nutr. Val. Org. and Inorg. P.) from balance experiments on a man, concluded that phosphorus and nitrogen metabolism need not run parallel, and also that the organism has not the same tendency to establish a phosphorus equilibrium that it has a nitrogen equilibrium, regarding which conclusions there is no doubt, since they simply signify that the organism can store phosphorus in the bones in large measure irrespective of the status of the nitrogen metabolism.

Lüthje and Berger (1904) reported results of five balance experiments with human beings having for their object the study of nitrogen, phosphorus and calcium metabolism in convalescents from typhus fever. Data from this work are on the following page.

In these experiments the object was to bring about maximum nitrogen retention, and then, by a comparison of the constituents of the food and excreta, to determine the form in which the nitrogen had been stored. The authors' computations were based on Katz's analyses of muscle and Zalesky's analyses of bone.

AVERAGE DAILY RETENTION OF NITROGEN, CALCIUM AND PHOSPHORUS BY MATURE MEN ON HEAVY FEEDING—Grams

Condition of subject	Diet	N Intake	P_2O_5 Intake	CaO Intake	N Balance	P_2O_5 Balance	CaO Balance	Weight of subject	Length of period in days
Typhus convalescent, age 30 years, reduced state	Milk, nutrose, sugar	40.246	10.887	5.740	+10.999	+2.832	+1.702	46.9 49.6	10
Typhus convalescent, age 24 years, well nourished	Milk, nutrose, sugar, zwieback	28.337	8.052	5.628	+5.165	+1.291	+0.741	63.3 66.3	12
Typhus convalescent, same as in first period, 16 days later	Milk, sugar, nutrose	54.583	12.385	7.760	+11.419	+1.255	+0.454	57.2 58.1	7
Normal	Milk, sugar, nutrose	27.337	9.305	5.339	+4.566	+3.381	+1.637	77.5 77.0	7
Normal; same as in first and third periods, after recovery	Milk, sugar, nutrose	57.187	12.497	5.910	+6.768	+1.747	+0.144	59.2 61.7	10

From the above data Lüthje and Berger compute that in periods 1 and 2 nitrogen, calcium and phosphorus were retained in proportion for the formation of flesh and bone; that in period 3 there was nitrogen retention without the corresponding quantity of phosphorus; and that in periods 4 and 5 there was phosphorus retention in excess of that which could be used with the other food constituents in the formation of flesh and bone.

They conclude, therefore, that with a large retention of nitrogen in a relatively short time, there is usually a quantity of phosphorus retained which corresponds to the nitrogen as does the phosphorus of flesh to the nitrogen of flesh; but there can also be an excess of nitrogen retained, and this is utilized in a different way, perhaps in the form of albumin, as a dead cell-inclusion, corresponding to the cell-deposit of glycogen and fat; and finally, in other cases, more phosphorus may be retained than that corresponding to the relation of nitrogen to phosphorus in flesh.

L. F. Meyer (1904a, 1904b) found, in balance experiments with dogs, that nitrogen could be retained from proteins which were so poor in phosphorus as to be incapable of maintaining phosphorus equilibrium. His data show, however, that the nitrogen retention was greater when the phosphorus balance was positive than when it was negative, the nitrogen intake remaining more nearly constant than the phosphorus. Meyer also notes the inclination of the organism to store phosphorus ingested in excess of the maintenance requirement, rather than to maintain an equilibrium, as is the case with regard to nitrogen.

Gumpert (1905) (see Sanatogen, feeding exp.) shows, in periods of 3 and 4 days, a retention of P_2O_5 of 0.143 and 0.600 gm. coincident with a loss of CaO of 0.307 and 0.244 gm.

Trowbridge and Woodman (1909) found that young, growing steers continued to grow in height, and to build up skeleton even when losing in weight, but the extent to which this involved redistribution of body constituents was not shown.

A large measure of independence of growth of skeleton and soft parts has been demonstrated by Fleischner (1906) with infants; by Waters (1908, 1909, 1909-10) with cattle, and by Aron (1910b) with dogs.

Kinberg (1911), in a study of nitrogen hunger, considered the proportions of nitrogen, sulphur and phosphorus in the urine. These relations varied irregularly throughout the period, but within comparatively narrow limits, viz., $N:H_2SO_4$ as 5.4—5.6:1 and $N:P_2O_5$ as 4.6—6.6:1.

Lipschütz (1911a) and many others express the opinion that in case of lack of a required element in the food, the body takes from less important parts to supply the more important. An important observation of recent date, in this field, is that of Gregersen (1911) who determined in metabolism experiments with rats that even with an abundant intake of phosphorus in assimilable form no phosphorus is retained from a *nitrogen-free* diet, thus suggesting a complete final dependence of the metabolism of phosphorus upon that of nitrogen.

Summary. From a consideration of the above notes we are able to understand that nitrogen and sulphur are somewhat closely interdependent, since they occur associated in the same compounds; phosphorus is to a considerable extent independent of nitrogen because of its relative abundance in the skeleton, while calcium is still more independent of nitrogen because of the poverty of the nitrogenous soft parts in calcium. Phosphorus is to some extent independent of calcium because of its association with nitrogen in the soft parts, but calcium is closely dependent on phosphorus because it is not stored in considerable amounts except as combined with phosphorus.

We must regard with considerable skepticism attempts to determine with much particularity the sources of excreted constituents by their relative amounts.

METABOLISM EXPERIMENTS WITH INORGANIC PHOSPHATES

J. Lehmann (1859) found in balance experiments with a calf that alkaline earth phosphates could be absorbed and retained. He concluded that many foods were lacking in bone-forming constituents, and that hay was the best bone-forming food.

Von Gohren (1861) conducted a balance experiment with a lamb on a ration of meadow hay, to which was added, in one period, calcium and magnesium phosphates. Data from this test are below.

AVERAGE DAILY BALANCE DATA FROM A LAMB ON A RATION OF MEADOW HAY WITH AND WITHOUT ADDED CALCIUM AND MAGNESIUM PHOSPHATES—Grams

Period and days	Ration	Food CaO	Food MgO	Food P_2O_5	Balance CaO	Balance MgO	Balance P_2O_5
I—7 days..	Meadow hay	7.081	2.395	3.187	+0.053	+0.164	+0.227
II—6 days..	Meadow hay, 10 gm. alkaline earth phosphates	10.421	2.428	7.440	+1.183	+0.275	+1.821

These data show that lambs will digest and retain very much more calcium, magnesium and phosphorus than was present in this meadow hay, if these elements be added to the hay as alkaline earth phosphates.

Two lots of lambs, of four each, were fed on these same rations for 45 days. The lot which received the phosphates gained in live weight 7.2 percent more than the one which received no phosphates. VonGohren noted that the urine of lambs is practically free from phosphorus and that the calcium also is found mostly in the feces.

Blondlot (1861) states that the administration of doses of 0.125 gm. sodium hypophosphite produces no phosphorous acid test in the urine, but that doses of 0.50 gm. give the characteristic green flame.

Gamgee, Priestley and Larmuth (1876-77) compared the sodium salts of pyro-, ortho- and meta-phosphoric acids by subcutaneous, intravenous and oral administration to frogs, rabbits and dogs. The ortho- salt was found to be inert, the pyro- salt markedly poisonous to the heart, when introduced into the circulation, and the meta- salt also poisonous but to a less marked degree.

Paquelin and Joly (1877) administered 2 gm. of sodium pyrophosphate daily for 5 days to a woman, and found during this period and the following 5 days that apparently all of the pyrophospho-

ric acid was eliminated in the urine unchanged. The sodium pyrophosphate had a slight diuretic effect. One qualifying circumstance, however, requires mention. The diet was not maintained entirely uniform during this experiment.

Paquelin and Joly (1878) administered to a woman during 5 days a total of 5 gm. of sodium hypophosphite. They concluded that the hypophosphites also are excreted unchanged in the urine, and that they have a diuretic effect.

Vermeulen (1884) studied the physiological action of hypophosphites, but without important results. He believes that they pass through the body unchanged. He determined hypophosphites in urine by first removing the phosphates by uranium precipitation and then determining total phosphates in a $KClO_3$+HCl digest of the filtrate.

J. Neumann (1893b) published results of two calf-feeding experiments, in one of which calcium phosphate, and the other calcium carbonate, was added to a skim milk diet. The calf used in the first experiment was 5½ weeks old, and its weight at the beginning of the experiment was 65.63 kg. The calf used in the second trial was 8 weeks old, and weighed 80.87 kg. at the beginning.

AVERAGE DAILY CALCIUM AND PHOSPHORUS BALANCES WITH CALVES ON A DIET OF SKIM MILK AND MINERAL SUPPLEMENTS—Grams

Date of periods	CaO Intake	CaO Outgo	CaO Balance	P_2O_5 Intake	P_2O_5 Outgo	P_2O_5 Balance	Diet
Sept. 10-14..	24.63	12.86	+11.77	30.46	14.91	+15.55	15000 gm. skim milk.
Sept. 15-16..	27.38	14.42	+12.96	32.83	16.87	+15.96	Same plus 7.5 gm. calcium phosphate.
Sept. 17-19..	29.19	16.77	+12.42	34.33	18.39	+15.94	Same plus 12 gm. calcium phosphate.
Sept. 29-30..	26.252	14.562	+11.690	34.039	19.511	+14.528	16000 gm. skim milk.
Oct. 1-2....	27.478	14.854	+12.624	33.863	19.712	+14.151	16000 gm. skim milk.
Oct. 3-7....	30.008	15.820	+14.188	33.980	19.327	+14.653	Same plus 7.5 gm. calcium carbonate.
Oct. 8-9....	26.407	15.285	+11.122	34.240	19.696	+14.544	16000 gm. skim milk.
Oct. 10-14..	26.412	14.776	+11.636	32.247	19.947	+14.300	16000 gm. skim milk.

Thus it appears that both calcium carbonate and phosphate, when added to skim milk, are digested and, in considerable measure, retained by the young calf; and further that calcium carbonate increased, not only the calcium storage, but also the phosphorus retention. Neither the calcium nor the phosphorus of the phosphate were so well retained as the same elements in the milk, but the calcium of the carbonate was retained in about the same proportion as the calcium of the milk. It was found that both of these mineral supplements tended to reduce the gain in live weight.

Weiske (1895b) mentions experiments by Graffenberger showing that on an oat ration rabbits digested a little more protein, fat, crude fiber and nitrogen-free extract without tricalcic phosphate than when this salt was added to the diet; and also experiments of his own where calcium carbonate was added to a ration of meadow hay, with rabbits, in which the mineral supplement seems to have reduced to a slight extent (1.35 percent) the digestibility of the protein, but to have increased to the extent of 10.11 percent the digestibility of the nitrogen-free extract.

Boddaert (1896) found calcium and sodium hypophosphites rapidly excreted, apparently as such, in the urine, whether administered *per os* or subcutaneously, with rabbits, dogs and men.

Massol and Gamel (1901) added sodium phosphate to a solution of calcium hypophosphite. The solution was then made alkaline, and a precipitate of tricalcium phosphate was formed, leaving sodium hypophosphite in solution. The same reaction, they state, takes place in the intestine, and the tricalcic phosphate is lost to the organism. The sodium hypophosphite is absorbed, and excreted unchanged by the kidneys, there being no oxidation of phosphorous acid. Thus calcium hypophosphite removes phosphorus from the system in proportion to the amount fed.

Panzer (1902), in studying the fate of calcium hypophosphite in the body, reached conclusions by the feeding of the compound, and then by qualitative tests (the green flame with nascent hydrogen, and the brown silver phosphide precipitate) in the urine, feces, blood and organs. The tests were made in part on a man and in part on dogs.

Panzer decided that if the methods were adequate to this investigation calcium hypophosphite fed to a dog is quickly and almost completely absorbed, passes through the organism without being held back anywhere, and is completely eliminated within 24 hours.

Martinet (1902a) says that hyperacidity of the urine accompanied by abnormally small amount of phosphates is frequently an index of hypochlorhydria in the stomach, and that in such cases the administration of phosphoric acid may promote digestion and check fermentation by its eupeptic and antiseptic action.

In a later article (1905) Martinet writes that by the use of phosphoric acid in 48 cases of dyspepsia, 32 cures have been accomplished, the liver also being benefited; urea excretion is increased; indican disappears and glycosuria of hepatic origin is relieved; also the hepato-pancreatic function is stimulated; intestinal functions are regulated, and diarrhoea suppressed. Treatment with sodium carbonate inhibits the digestive functions, especially of the stomach, while the phosphoric acid treatment, on the contrary, stimulates these functions.

Gouin and Andouard (1902-3) conducted digestion experiments on a heifer, having for their object a study of the effects on metabolism of certain inorganic salts. The basal ration was composed of milk, rice meal, clover, peas, and oats. Acid potassium phosphate, in the proportion of 5 grams per 100 kg. live weight, was fed during 8 weeks. Benefit was thought to have resulted. The feeding of 150 grams of powdered bone per day, equivalent to 28.29 gm. P_2O_5, greatly increased the urinary phosphorus, and had a depressing effect on the digestion of protein, carbohydrates and fat.

Cautru (1903, 1904a, 1904b) fed pure phosphoric acid in considerable quantities to guinea pigs, dogs, ducks, horses and human beings, during protracted periods, to determine limits of toleration and therapeutic effects. In large doses, even, the acid is innocuous, and is recommended by Cautru for use in such morbid states as are characterized by demineralization and hypoacidity of the urine. As much as 2-4 gm. daily were fed to human beings for more than 5 years; a dog weighing 8.5 kg. was given gradually increasing doses up to 3 gm. for one month; a duck was given one gram per day; horses were given 30-100 gm. daily; two guinea pigs weighing 350 gm. received 0.5-1.0 gm. daily, etc.

Köhler *et al.* (1904), in experiments with yearling lambs, found that when added to a ration containing comparatively little mineral matter tricalcic phosphate was retained in larger proportion to the intake than were dicalcic phosphate, precipitated bone earths (di- and tri-salts), or calcined bone. After making this observation, he determined with a 6-months-old lamb that the reason the dicalcic phosphate was not so well retained as the tricalcic salt was its lack of calcium. When additional calcium was provided, as calcium lactate, the phosphorus of the dicalcic salt was much more efficiently retained than that of the tricalcic phosphate.

Of the phosphorus of the precipitated bone earths the retention was 13.1 percent, of the calcined bones 14.2 percent, of the dicalcic phosphate 26 percent and of the tricalcic salt 35.5 percent. With the younger lamb the phosphorus of the tricalcic phosphate was retained to the extent of 38.6 percent of the intake, of the dicalcic phosphate, 35 percent when fed alone, and 54.7 percent when fed with calcium lactate.

Joulie (1904) administered phosphoric acid in rheumatism of horses. The dose was 10 c.c. phosphoric acid (sp. gr. 1.35) diluted to a liter. He states that such introduction of phosphoric acid diminishes the alkalinity of the blood, and increases the elimination of calcium phosphate by the kidneys.

Kramer (1907) investigated the effects of ingestion of calcium phosphate on the laxative tendency of beet leaves when fed to cows. It is usually credited with preventing a laxative effect, but in this case the beet leaves were not sufficiently laxative to permit of this observation.

Köhler, Honcamp and Eisenkolbe (1907) reported results on further tests of inorganic phosphates with lambs. The authors conclude that the phosphorus of the dicalcic salt is slightly better absorbed and retained than the tricalcic salt, and that the addition of calcium lactate or calcium carbonate is without influence on the degree of retention of the phosphorus. The results of these tests are so variable that it seems to the writers unwise to draw conclusions from them.

W. Müller and vonWendt (1908) found that precipitated calcium phosphate fed to cattle suffering with diarrhoea, from eating partially decomposed beet leaves, served to allay the symptoms, while calcium carbonate accentuated the difficulty. The authors explain the unfavorable effect of the carbonate as due to the neutralization of the acid products of bacterial growth, thus favoring further growth. Oxalic acid was shown not to be the cause of the indigestion.

Aron and Sebauer (1908) concluded from feeding experiments with rabbits and dogs, using calcium-poor rations, to which in some cases bone meal, calcium phosphate or calcium carbonate was added, that the lack of these calcium compounds affected, in noteworthy degree, only the bones, these being below normal in dry substance and in the calcium content of the dry matter, the reduction of calcium content of the ash being considered immaterial. The calcium content of the flesh and blood shows no reduction, while the calcium content of the brain is reduced but little.

Dibbelt (1909) conducted metabolism experiments with dogs, in which dicalcic phosphate, sodium chloride and magnesium sulphate were added, in different periods, to a standard basal ration. A part of the data are below.

AVERAGE DAILY CALCIUM AND PHOSPHORUS BALANCES WITH DOGS, AS AFFECTED BY INORGANIC SALTS—Grams

Exp. No.	Length of period in days	Gain in weight	CaO Intake	CaO Retention	P_2O_5 Intake	P_2O_5 Retention	Diet and treatment
1	15	100	0.0500	−0.0478	2.3124	0.6181	Horse meat and pork fat.
2	10	80	0.0500	+0.010	2.3124	1.1882	Horse meat and pork fat; immediately following Exp. No. 1.
3	9		0.0500	−0.001	2.3124	0.7384	Horse meat, pork fat and 12 gm. salt.
4	11		0.2178	+0.1388	2.5188	1.0989	Horse meat, pork fat and 0.5 gm. dicalcium phosphate.
5	7	3.57	0.0150	+0.003	0.6937	0 1907	Horse meat, fat and salt.
6	23	9.78	0.0160	+0.0062	0.7400	0.3618	Horse meat, fat, salt and magnesium sulphate.

In Exp. No. 1 it appeared that horse meat and pork fat were deficient in calcium, but in Exp. No. 2, with the same diet and same animal, it seemed that the dog had accomplished an adjustment to this diet. The result in No. 3, where salt was fed, was essentially the same, so far as calcium is concerned; at least it did not differ from No. 2 as much as No. 2 differed from No. 1. In Exp. No. 4, however, there was a marked calcium storage coincident with the feeding of dicalcium phosphate.

Experiments 5 and 6 were on another dog. There appeared to be an effect by the magnesium sulphate to increase the storage of calcium and phosphorus, but the evidence must be regarded as inconclusive on this point. The preliminary period was short. Some days after the conclusion of Exp. 6 this dog was killed, and the calcium content of its tissues was compared with the same from another dog which had received the same ration except that dicalcium phosphate replaced magnesium sulphate. The soft parts of the dog receiving magnesium sulphate were found much richer, but the bones poorer, in calcium, than those of the dog which received dicalcium phosphate. These differences the author explains by assuming that the magnesium sulphate had reacted with the soluble calcium phosphates to form the comparatively insoluble calcium sulphate.

Dibbelt conducted other experiments in the artificial production of rachitic conditions, and concluded that the principal difference between these conditions and rachitis is in the cause of the calcium deficiency, this being due in the latter case especially to anomalies of absorption and secretion, rather than to calcium shortage in the food as a first cause.

Crawford (1910) fed sodium metaphosphate, sodium pyrophosphate and sodium orthophosphate to rabbits in a study of cottonseed meal poisoning. The feeding of 2 gm. of the metaphosphate daily for two days caused the death of the subject, as also did the feeding of 0.5 gm. of the pyrophosphate per day for 7 days. The dosage was enormous. The author's conclusion that cottonseed meal poisoning was due to pyrophosphates has not withstood criticism.

Delaini (1911) submits data showing that human beings and dogs eliminate in the urine practically the whole amount of hypophosphite of sodium administered either *per os* or subcutaneously, but that rabbits otherwise dispose of perhaps 20 percent of the intake.

Patta (1910) administered to a dog, by injection, varying doses of sodium hypophosphite. If administered in large amounts about half of all introduced can be recovered, unoxidized, in the urine;

when smaller amounts are administered, the proportion recovered is less, being as low as one-sixth at times. Hence it is maintained that the phosphorus of hypophosphites can be retained by the organism.

Starkenstein (1911) theorizes to the effect that the reason that pyrophosphoric acid and metaphosphoric acid are poisonous when injected into the organism, while orthophosphoric acid is not, is that these acids are formed from orthophosphoric acid by condensation of molecules, and loss of water. Experiment showed that if orthophosphoric acid be used in sufficient amount and concentration, it also poisons—10 c.c. of 14 percent Na_2HPO_4, injected, produces the same effect as 2 c.c. of 5 percent pyrophosphate solution. The poisonous salts are more alkaline. Is the poison due to alkalinity? Blake found that they are more easily dissociated, which would mean greater alkalinity. Dissociation tests of the acids by reaction toward different indicators, by conductivity, and by heat of reaction all show that the pyrophosphoric acid has higher true acidity than the orthophosphoric acid. Two of the H^+ of the pyrophosphoric acid split off as easily as one of the orthophosphoric acid; therefore probably the tetrapyrophosphate of sodium dissociates to give as much OH^- as does the tertiary salt of the ortho acid.

Withers and Ray (1913) submit evidence controverting the idea that cottonseed meal poisoning is due to pyrophosphates.

See also Etzinger (1874) on digestibility of bones by dogs; Charrin and Desgrez (1896) on subcutaneous injection of salts, including sodium phosphate; Vosgien and Géroline (1899) on retention of inorganic phosphates by rabbits; Charrin (1905) on subcutaneous injection of salts, including sodium phosphate; Cook (1909, Met. Phytin), and Draeger (1911) on the assimilation of calcium phosphates.

MISCELLANEOUS EFFECTS OF INORGANIC PHOSPHATES ON GROWTH

Graffenberger (1893) found that the feeding of calcium phosphate to rabbits did not increase the calcium and phosphorus content of their litters.

Knauthe (1898) submits data from experiments with carp, showing that the addition of meat ash to rations of meat meal and corn meal, or meat meal and rice meal, serves to increase both nitrogen retention and gain in weight.

W. P. Wheeler (1903) reported more efficient use of food, and more rapid growth of chicks, from the addition of rock phosphate to a ration of vegetable foods. As a source of calcium and phosphorus for chicks, however, Wheeler recommends raw or cooked bone.

Klien (1908) found, in feeding experiments on growing pigs, that when added to a ration of milk, potatoes, barley and rye, calcium carbonate had about the same value as calcium phosphate in causing increase of weight.

Moore, Roef and Knowles (1908) found that newts would respond to the presence of both acid and alkali phosphates in the water in which they were kept, by increased growth, provided the salts were present in certain optimum concentrations. In excessive amounts monosodium phosphate was depressant, the disodium salt producing excitation.

The same salts were fed to guinea pigs and dogs in quantities sufficient to cause pathological symptoms, and the histological condition of the organs and tissues is described.

For other materials on the effects of phosphates on general growth see Mai (1869), W. Cohn (1870), J. Lehmann (1873, 1877), Passon (1905), Carlier (1907, 1909) and Forbes and associates (1914).

Summary: Alkaline earth phosphates can be absorbed and retained by sheep when added to a ration of hay.

Calcium phosphate and calcium carbonate can be absorbed and retained by the calf when added to a skim milk diet. Calcium carbonate, under these circumstances, increases the phosphorus retention, calcium thus appearing to be a limiting factor in the use of the phosphorus of milk. Both the carbonate and the phosphate tend to reduce the gain in live weight.

Tricalcic phosphate depressed to a slight extent digestibility of oats by rabbits, and of a mixed ration of milk, grain and green feeds by a heifer. Calcium carbonate seems to depress the digestibility of protein and to increase the digestibility of nitrogen-free extract of oats with rabbits.

Phosphoric acid has been found to stimulate gastric functions in cases of hypochlorhydric dyspepsia.

By subcutaneous injection of phosphates it is learned that the ortho-salts, in moderate amounts, are inert; the pyro-salts are markedly poisonous; while the meta-salts are also poisonous, but to a less marked extent.

Lack of consistent results makes difficult the use of data on the comparative values of the various calcium salts fed to live stock.

We have very little evidence that the inorganic salts of other than the ortho-phosphoric acid are of value as bearers either of phosphorus or of base. The hypophosphites especially are, throughout therapeutic literature, spoken of as inactive.

In contradistinction to the effects of phosphates on the bones the ingestion of inorganic phosphates produces slight effect on body growth in general.

METABOLISM OF NUCLEOPROTEINS AND NUCLEIC ACIDS *

GENERAL DISCUSSION

Anabolic Processes. It is evident from various observations that the animal organism is capable of building up for itself nuclear material from other forms of protein. The first definite evidence of such synthesis in the body was that from Miescher's (1881, 1896) observations on Rhine salmon, where it was concluded that the nuclein-rich reproductive substance of these fish must form from the material of the muscles, for nearly the entire development of the reproductive organs and their sperm and ova takes place while the fish are taking no food, the fibres of the body muscles losing much of their protein at the same time. This view with regard to salmon was strengthened by the investigations of Paton and his associates when they found that the amounts of phosphorus lost by the body muscles account quantitatively for the gain of phosphorus in the ovaries and testes. (Paton, *et al.*, 1897-8; Paton, 1898). According to Milroy (1908), it is not true of herring that the genitalia derive their protein from the protein of body muscle, neither the protein nor the phosphorus figures indicating such a relation in his examinations. These studies were inconclusive because of the lack of complete chemical accounting for the entire fish.

Building up nuclein from purin-free protein must, according to the reports of Burián and Schur (1897), take place in the bodies of suckling animals. From xanthin-base nitrogen and nuclein phosphorus determinations on the body substance of suckling pups at different ages, and on the mother dog's milk, it appeared that the increase of nuclein in the young animal is too great to be accounted for by the very small amount of nuclein taken in the milk.

Schmoll (1904) discusses the chemical origin of leucocytes, considering the question of the synthesis of nucleins by the adult human organism. Leucocyte counts in the blood, and uric acid and purin base determinations in the urine, while patients were on a normal mixed diet, or on diets rich or very poor in purins, are used as evidence of the synthesis of leucocytes (nuclein) from the albumin of the food without the necessity for food purins.

McCollum (1909) also considered nuclein synthesis in rats. The subjects were fed in groups of 3 on (1) normal food, (2) a ration free from organic phosphorus and from purins, (3) a ration such as the last with purins from liver and hydrolyzed beef muscle added, or (4) with casein added to the basal ration. The bodies of some

* For general discussions see A Schittenhelm: Der Nucleinstoffwechsel; Oppenheimer's Handbuch, Vol. IV, 1st half, 489-539, also Brugsch and Schittenhelm (1910), and Schaumann (1910).

were examined as to percent of skeleton and percent of fat-free tissue, but the evidence as to the synthetic powers of the organism is mainly the rate of gain in live weight of the animals. He concluded that the phosphorus needed by an animal for nuclein formation can be drawn from inorganic phosphates, and that the animal has the power to synthesize the purin base necessary for its nuclein formation from some complexes contained in the protein molecule, and does not necessarily use purin bases of exogenous origin for this purpose. Complete chemical accountings for the bodies of the rats would have been required to establish these points.

Other investigations involving the subject of nuclein synthesis are those which are considered, in the section on The Nutritive Values of Organic and Inorganic Phosphorus, as evidence of the production of growth from rations which are free from inorganic phosphorus.

Evidence of synthetic changes in the nuclear material of developing eggs of silk-worms has been submitted by Tichomiroff (1885), and of hens by A. Kossel (1885, 1886). On the other hand, Shackell (1911) was unable to find in the early stages of developing sea-urchin eggs any convincing evidence of the synthesis of nuclear material from the alcohol-soluble substances of the cytoplasm; and this corresponds with the observations of Masing (1910), who compared unfertilized sea-urchin eggs, or those which, being fertilized, had just formed the membrane, with others which had developed to the morula stage, where there are 500-1000 cells. The nuclear mass has at that time multiplied nearly 100-fold, but the nucleic acid content was not found to be any greater than in the unfertilized eggs. Later (1911b) he made similar examination of the successive stages of the embryos of rabbits, and of the livers of embryonal rabbits. Both the whole embryo and the embryo liver showed decreasing percentage content of nuclein as development progressed, though the absolute amount increased. Sections of the livers showed under the microscope a corresponding decrease in the *relative* size of the nucleus. Masing's work, then, makes it appear that there is a large supply of nuclear material at the start to provide for growth.

There is little evidence as to the habit of the body with regard to the details of anabolism during growth and repair. There is abundant evidence that the organs contain within themselves enzymes which can break down nucleins, but whether they do in fact break them down to the stage of free purins and phosphoric acid before building them into new cellular matter is not known. It may be advantageous and habitual for the cleavage, whether in the digestive tract or in the tissues, to be stopped at an earlier stage. The

investigations of Taylor (1907) and of Robertson (1907, 1909a, 1911) indicate that syntheses may, under the right circumstances, be brought about by the same enzymes which under other circumstances cause cleavage.

The attempts which have been made at artificial synthesis of nucleoproteins or nucleins are reported and discussed in the chapter on the chemistry of these compounds.

Katabolic Processes. Three distinct methods of experimental study have been employed in attempts to learn of the extent to which nucleoproteins are broken down in the life processes of the organism, the transformations involved and the places at which they occur.

First, isolated enzymes or digestive secretions from the alimentary tract have been allowed to act on the substances in question under controlled conditions and at favorable temperatures, the extent and nature of the change taking place in the digestive tract of the animal being judged by the results of these artificial digestions, *in vitro*. To this may be added the consideration of changes which may be brought about by such bacteria as are found in the intestine. It is to be recognized that observations of this kind lose somewhat in significance from being made under artificial conditions; but, on the other hand, there is an advantage in the limitation of variable or unknown factors.

A second type of studies made outside the body, and therefore under unnatural conditions, but probably being to an important degree indicative of the body processes, has been followed extensively in recent years. We refer to studies with comminuted organs in suspension, or with water extracts of organs, as to their autodigestion, especially as related to purins, and their capacities to transform added nucleic acids or their derivatives. Evidently the organs and tissues generally have within themselves enzymes, or the means for producing them, by which they may break down and transform their own nucleoproteins, or partially digested nucleoproteins or nucleic acids which may be brought to them.

The third method of study makes observations of the actual results in living subjects from introduction of the substance, either in the diet or by some form of injection.

DIGESTION STUDIES WITH ENZYMES FROM THE ALIMENTARY TRACT

Popoff (1894) concluded from digestions of thymus gland with ferment preparations that "Solution of nuclein material occurs only very slightly in the stomach, but to a considerable extent in the intestine, through the agency of the pancreatic juice. Here the nu-

clein bodies as such are taken into solution, so that it may be inferred that they are also resorbed as such." Very little inorganic phosphorus appeared in the solution.

Milroy (1896) found most of the phosphorus from natural or artificial nucleins in organic form after trypsin digestion.

A. Neumann's (1898) examination of the α- and β-nucleic acids and nucleothyminic acid showed that none of these were attacked by pepsin-hydrochloric acid, but that they were dissolved by alkaline intestinal fluids.

Umber (1901) made long peptic and tryptic digestions of the nucleoprotein from pancreas. About nine-tenths of the nucleoprotein passed into solution under the influence of the pepsin. The pepsin first brought about a separation of a protein from a pentose-rich nucleic acid, which was soluble and could be absorbed, but which was not further broken down by pepsin. The digestion of the protein component, after being split off from the nucleic acid, proceeds in the ordinary way with the formation of primary and secondary albumoses, peptone and lower cleavage products. Trypsin had a like effect to that of pepsin, and required less time.

Araki (1903a) carried out artificial tests which seemed to indicate that the nuclear substance of the red corpuscles of bird's blood is rather quickly dissolved by trypsin; that there is in thymus extract an enzyme which has a like but slower action; also that by both trypsin and the thymus extract nucleic acid is changed from the less soluble (gelatinizing) form which Kossel and Neumann called α-acid to the more readily soluble (non-gelatinizing) β-acid, and no further digestion occurs except after long-continued action; and that erepsin splits nuclein and dissolves nucleic acid.

Nakayama (1904) compared the action of erepsin from a dog with that of trypsin and of weakly alkaline extracts from the intestines of cattle and rabbits. Commercial trypsins did not digest nucleic acids. The erepsin slowly digested the sodium salts of nucleic acids from the intestine of cattle, from thymus, from the spleen of cattle, and from the spermatozoa of *Muraenosox cinereus.* In each case phosphoric acid was found in the resulting solution. The extract of intestine acted on the nucleic acid much as did the erepsin.

In connection with the study of enzyme action on caseinogen Plimmer and Bayliss (1906) tested the artificial digestion of yeast nuclein with trypsin, and found about four-fifths of its phosphorus in solution as phosphoric acid after 21 days.

Mitra (1911) considered the age at which nuclease appears in the stomach of the infant. An infant a year old was fed on milk, on milk with flour and on porridge made from legumes; and at intervals of 0.5, 1, 1.5 and 2 hours after ingestion portions were removed from the stomach and tested with connective tissue and muscle fibre. No nuclease nor connectivase was found. A similar experiment on a child of fifteen months seemed to show the presence of both.

Levene and Medigreceanu (1911c) have made various kinds of nucleic acid digestion tests, among them some such as are now under discussion. Inosin, guanosin, cytidin, guanylic acid, pyrimidin nucleotides, yeast nucleic acid and thymus nucleic acid were studied. The glucosides (inosin, guanosin and cytidin) were not changed in the neutralized gastric, pancreatic or intestinal juices. The mononucleotides (guanylic acid and the pyrimidin nucleotides) were not affected by gastric or pancreatic juice; but with intestinal juice changes were produced which are interpreted as showing that phosphoric acid was split off from the guanosin or pyrimidin complex, with no further change of these complexes. The action was much slower in the case of the pyrimidin nucleotides than in that of the guanylic acid. The complex nucleic acids (yeast nucleic acid and thymus nucleic acid) were little changed by gastric or pancreatic juice, but considerably (rapidly in the case of the yeast nucleic acid) by intestinal juice. The changes are interpreted as indicating a cleavage into phosphoric acid and an organic complex, but no reducing substance (carbohydrate) was set free. These experiments seem to indicate that nucleic acids are not digested or absorbed by the stomach, but that in the intestine phosphoric acid is split off under the action of intestinal juice. The going into solution which others had observed as apparently brought about by trypsin may have been without this splitting, being simply such a change as Araki noted.

According to Schaumann, "Schittenhelm (Arch. f. klin. Med.81, 1904, 423) found that in disease of the pancreas the digestion of nuclein suffers, and he thinks that the chemical experiments correspond with the microscopical observations. In considering the latter, he points to the observations of Schmidt, who showed long ago that in failure of pancreatic ferment unchanged cell nuclei of the food are passed with the feces."

Abderhalden and Schittenhelm's (1906a) artificial digestions of the sodium salt of α-thymonucleic acid with the juices of the digestive tract, and with water extracts of pancreas and intestine, showed no determinable change by the gastric juice, and with the

pancreatic juice none which went far enough to yield purin bases, though there was some unknown kind of alteration which made the nucleic acid more readily soluble, and increased the amount of dialyzable matter. The extracts of pancreas and intestine, however, produced an abundance of purin bases and a clear solution. Interpreted as indications of the place in which cleavage occurs within the body, these experiments point to the understanding that nucleic acids do not undergo deep cleavage by digestive enzymes within the intestine but only in and beyond the intestinal wall.

EFFECTS OF BACTERIA IN THE ALIMENTARY TRACT

Bacteria in the digestive tract, especially in the large intestine, and perhaps also such as are introduced with the food, may have considerable to do with the disposition of nucleins. These microörganisms show the power, not only to cleave nucleins in the ways shown above, but also to change amino-purins to oxypurins, even as far as uric acid. Doubtless they produce such effects, as they remain for considerable time in contact with the food material.

It should be remembered that these bacteria further complicate the studies of nuclein digestion because the purins of the feces may come from their bodies, Schittenhelm and Tollens say to the extent of 31.3 percent. Such purins would be the result of constructive as well as destructive activities of the bacteria.

Schittenhelm (1903) has shown that nearly all of the nuclein substance of feces disappears as they undergo autoputrefaction; and Schittenhelm and Schroeter (1903a, 1903b, 1904) showed that bacteria may bring about a deep cleavage of yeast nucleic acid.

Schaumann tells us that Emmerich and Low (Zeit. f. Hygiene 36, 1901, 9) found in pathogenic bacteria enzymes which were effective to dissolve, not only their own nucleoproteins, but also those of other species of bacteria.

Plenge (1903) showed that some bacteria have the power to liquify the sodium salt of α-nucleic acid from thymus and that the action is brought about by means of an enzyme.

Vegetable moulds were shown by Iwanoff (1903) to contain or produce an enzyme which completely cleaves nucleic acids.

Hahn and Geret (1900) found evidence of an enzyme in the expressed juice of yeast which has a cleaving action on proteins, including nucleoproteins, which is much like that of trypsin but calls for slightly acid solution. It frees the bases and amino-acids directly, without forming peptones, and but very little intermediary albumose. After one hour's digestion at 37°C. the greater part of the phosphorus was converted to the form of phosphoric acid. The enzyme is designated as yeast endotrypsin, and it is thought that it may play an important part in disassimilation.

FERMENTS OF INDIVIDUAL ORGANS

The enzymatic actions studied in various organs have included those of nucleases, guanase, adenase, xanthoxidase and uricase. All of these except the nucleases concern only the purin fraction of the compounds. Since the oxypurins, xanthin and hypoxanthin, are thought to be absorbable, and the amino-purins not, and since any processes concerned with the disposal of the nuclein substance may be of importance in the consideration of nucleins as foods, we are including a number of the many references to studies of the location of purin enzymes, but we discuss only those on nucleases, as having a direct bearing on the freeing of phosphorus from the molecule.

The most productive workers in this field have been Jones and Schittenhelm and their co-laborers. References are listed below. The article by Wells (1910) summarizes in detail the enzymes which had, at the time of his writing, been located in the organs of different animals. Nuclease was found in all organs tested, but other ferments were rather variously distributed, and it is noticed that species differ in this respect.

Pighini's (1910,1911) optical methods used in determining nucleic acid cleavage by blood serum are called in question by Amberg and Jones (1911a). They find no cleavage of thymus nucleic acid by blood sera; yeast nucleic acid, they say, is altered in some way, and perhaps decomposed, but without liberation of either phosphoric acid or purin bases.

A. J. Juschtschenko (1911) (see also Yushchenko, 1912) has studied the relative nuclease content of the blood, muscles and various organs of man, dog, horse, cow, rabbit, hen and pike-perch, by making inorganic phosphorus determinations on uniformly prepared solutions containing salt-water extracts of the organs and sodium nucleate solution, after the mixed solution had stood for 40-42 hours in a thermostat at 37-38°. The data reported show the milligrams of P_2O_5 set free from the nucleate by one gram of organ. The general conclusions from the work are thus expressed:

"Liver, kidney, spleen, pancreas, and thyroid gland contain significant quantities of nuclease; brain, suprarenals, lungs, and lymphatic glands contain smaller quantities; heart, blood, muscle and serum are poor in nuclease. The blood of dogs, rabbits and cattle is richer in nuclease than that of man. The livers of man, horse, cattle, rabbit and pike-perch are richer in nuclease than that of the dog. In most organs of young dogs the nuclease content is less than in the same organs of grown dogs. The organs of man are in general rich in nuclease."

Later (A. Juschtschenko, 1911), thyroidectomy was found to reduce the nuclease content of the organs and blood of young dogs and the blood of rabbits.

E. K. Marshall, Jr. (1913) has determined that the ferments of the thymus can not digest all of the nucleic acid of the gland, but leave a portion completely unaltered.

According to Levene and Medigreceanu (1911d), "there exist in the organism several enzymes, which act harmoniously, leading to the disintegration of nucleic acids. The function which hitherto has been ascribed to the 'nucleases' is in reality performed by at least three enzymes, or rather three groups of enzymes, which have to be designated by special names. The part of each enzyme is to render the nucleic acid molecule susceptible to the action of one of the other enzymes, thus producing successive disintegration."

Nucleinases are those enzymes which cause the dissolution of the nucleic acid molecule into nucleotides. Nucleinase is present in practically all organs and in the pancreatic juice. It is not present in gastric juice.

Nucleotidases split nucleotides into phosphoric acid and a carbohydrate-base complex. They are present in the plasma of all organs, and in the intestinal juice; they are not present in gastric or in pancreatic juice.

"Also in regard to *nucleotidases* the possibility is not excluded that there exists more than one enzyme of the same group, and this for the following reasons..... [There is] gradation in the stability of the nucleotides towards chemical agencies..... [and]..... towards enzymes. Thus, guanylic acid is hydrolyzed readily into phosphoric acid and guanosin by the plasma of the pancreatic gland, whereas there could not be ascertained the occurrence of the analogous cleavage of inosinic acid, of pyrimidin nucleotides, nor of the complex nucleic acids, through the action of the same plasma. On the other hand the cleavage takes place in all nucleotides under the action of the extract of the intestinal mucosa."

Nucleosidases split nucleosides (purin ribosides) into their components. They are present in the plasma of most organs examined but not present in the plasma of the pancreas, nor in gastric, pancreatic or intestinal juice.

"Pyrimidin Complexes. Comparatively little information is obtained regarding the mechanism through which these substances undergo disintegration in the animal organism. The only evidence of the possible existence of enzymes bringing about cleavage of these complexes may be found in the older observation of Levene, that in course of prolonged autolysis of organs, free pyrimidins are formed."

A viscosity method has been used by de la Blanchardière (1913) in investigation of nucleolytic enzyme activity. From such observations, made with organ extracts and pancreatic secretion, it is concluded that nuclease is not identical with any proteolytic enzyme; also that the processes of liquefying and of cleaving the nucleic acid are distinct, the work either of two different nucleases or of two different groups of the enzyme molecule.

References on organ tests: Horbaczewski, 1889, 1891a, 1891b, 1893, Schwiening, 1894; Spitzer, 1899; Kutscher, 1901; Araki, 1903a; Jones, 1904a, 1904b, 1904c; Jones and Partridge, 1904; Schittenhelm, 1904a, 1904b, 1905a, 1905b; Jones and Winternitz, 1905; Jones, 1905; Schenck, 1905; Burián, 1905; Sachs, 1905; Bloch, Bruno, 1906; Abderhalden and Schittenhelm—résumé of literature—1906a; Schittenhelm and Schmidt, 1906, 1907a, 1907b; Jones and Austrian, 1906, 1907a, 1907b; Arinkin, 1907; Mendel, L. B., and Mitchell, 1907-8; Jones, 1908; Steudel, 1908a, 1908b; Kunzel and Schittenhelm, 1908, 1909; Schittenhelm, 1908, 1909a, 1909b; Wells and Corper, 1909; Leonard and Jones, 1909; Rohdé and Jones, 1909; Miller and Jones, 1909; Straughn and Jones, 1909; Winternitz and Jones, 1909; Jones, 1910; Wells, 1910; Pighini, 1910, 1911; Amberg and Jones, 1911a, 1911b; Jones, 1911a, 1911b; A. J. Juschtschenko, 1911; A. Juschtschenko, 1911; Medigreceanu, 1911; Levene and Medigreceanu, 1911b, 1911d; Mihari, 1911; Corper, 1912; Schittenhelm and Wiener, 1912; Yushchenko, 1912; Levene and LaForge, 1913; de la Blanchardière, 1913; Marshall, 1913.

ANIMAL EXPERIMENTS ON THE DIGESTION OF NUCLEOPROTEINS AND NUCLEIC ACIDS

Loewi (1900, 1900-01) conducted metabolism experiments, mostly with human subjects, in which observations were made of the effects on excretion of adding various nuclein substances to a mixed diet. In the work reported in the first paper thymus gland was substituted for beef in an otherwise constant mixed diet with a subject suffering from myelogenic leukaemia, and with a normal subject; the effect of adding pancreas to a constant mixed diet was also studied; and a search was made for allantoin in human urine after the ingestion of pancreas, desiccated pancreas or thymus. It was concluded (in part) that: The excretion of uric acid in leukaemics is not different from that in normal individuals; there is diuresis. The ratio of uric acid to P_2O_5 does not increase with mathematical precision following thymus feeding. Both the items are increased by the gland. Increased katabolism does not occur, since the nitrogen figures return to normal shortly after discontinuing thymus feeding. No allantoin could be found in the samples of human urine examined.

The work reported in the second paper includes similar tests with salmon nuclein, pancreas nuclein, yeast nuclein, nucleic acid and "Nutrose" (a neutral sodium casein preparation from milk); also thymus was fed to a dog having ligated pancreatic ducts, and P_2O_5 was estimated in the excreta; and the uric acid excretion in the urine was compared in three subjects on the same ration.

AVERAGE DAILY NITROGEN AND PHOSPHORUS BALANCES, WITH A HUMAN BEING, AS AFFECTED BY NUCLEINS

Loewi (1900-01)—Grams

Period	No. of days	Ration	Intake		Output								Balance	
					Urine				Feces		Total			
			N	P_2O_5	N	P_2O_5	Urea N	Uric acid N	N	P_2O_5	N	P_2O_5	N	P_2O_5
EXPERIMENT I														
I	4	Standard diet	15.532	3.591	13.797	2.46	12.00	0.5533	1.96	0.94	15.757	3.40	−0.225	+0.19
II	1	Standard + 30 gm. salmon nuclein	20.857	7.077	15.960	3.73	14.00	1.0416	1.62	1.40	17.58	5.13	+3.277	+1.95
III	3	Standard	15.532	3.591	13.942	2.49	11.88	0.6583	1.51	0.72	15.452	3.21	+0.08	+0.38
IV	1	Standard + 20 gm. pancreas nuclein	18.694	5.337	14.672	3.04	12.32	1.5920	2.56	1.86	17.232	4.90	+1.462	+0.44
V	2	Standard	15.532	3.591	13.496	2.50	11.20	0.7665	2.22	1.06	15.716	3.57	−0.184	+0.025
VI	1	Standard + 30 gm. yeast nuclein	19.171	5.245	15.070	3.25	13.52	1.0836	1.68	1.04	16.75	4.29	+2.421	+0.955
VII	3	Standard	15.751	3.637	13.286	2.47	11.85	0.6346	1.86	0.92	15.146	3.39	+0.605	+0.25
VIII	1	Standard + 20 gm. nucleic acid	18.735	7.114	15.120	3.78	12.77	0.8568	1.74	1.76	16.86	5.54	+1.875	+1.574
IX	2	Standard	15.922	3.710	13.070	2.34	11.48	0.7014	1.95	1.20	15.02	3.54	+0.902	+0.170
EXPERIMENT III														
I	4	Standard	19.70	9.115	18.069	3.996	.....	.....	1.185	3.409	19.253	7.405	+0.5	+1.72
II	3	Standard + 5 gm. sodium nucleate	20.277	9.35	16.306	3.775	.....	.....	1.236	3.439	17.543	7.194	+2.8	+2.156
III	2	Standard	19.70	9.115	16.631	3.699	.....	.....	1.004	2.372	17.635	6.071	+2.06	+3.05
EXPERIMENT IV														
I	6	Standard	17.725	3.88	15.15	2.88	.....	.....	1.18	0.88	16.33	3.76	+1.39	+0.12
II	3	Standard + 30 gm. yeast preparation	21.325	4.151	15.97	2.72	.....	.....	1.60	0.98	17.03	3.70	+4.29	+0.45
III	3	Standard	17.873	4.029	14.97	2.92	.....	.....	1.69	0.89	16.66	3.81	+1.21	+0.22
EXPERIMENT V														
I	6	Standard	17.725	3.88	15.12	3.26	.....	.....	2.036	1.57	17.158	4.83	+0.567	−0.95
II	3	Standard + 15.5 gm. nutrose	19.810	4.28	16.524	3.36	.....	.....	2.678	2.09	19.202	5.45	+0.584	−1.17
III	4	Standard	17.873	4.03	16.012	3.48	.....	.....	2.158	1.47	18.18	4.95	−0.297	−0.92

Subject of experiment I, age 27, weight 70 kg., standard ration 150 gm. beef, 120 gm. butter, 285 gm. white bread (dry), 6 eggs, 50 c.c. cream, 300 c.c. coffee, 300 c.c. wine, 600 c.c. beer.
Standard diet, Experiment III, 2,750 c.c. milk, 100 gm. sugar, 100 gm. cheese, 30 gm. (or 25 gm.) butter.
Subject of Experiment IV, age 25, weight 70 kg., standard diet 200 gm. sirloin, 285 gm. white bread, 150 gm. butter, 6 eggs, 700 c.c. coffee, 1500 c.c. beer.
Subject of Experiment V, 25 years, weight 74.5 kg., standard diet as in Exp. IV.

Conclusions (in part). "The nucleins of the food are in part cleaved in the intestine; the P_2O_5 of the cleaved fraction passes into the feces, the nitrogenous fraction is resorbed. The larger portion uncleaved is resorbed *in toto*, whereby the P_2O_5 remains in organic combination."

"It is possible by nuclein feeding to cause a retention of nitrogen and phosphorus in the body in the same proportions that these substances are present in the ingested nuclein."

"Nuclein superposition, under certain conditions, encourages nitrogen as well as phosphorus retention."

"Excepting the uric acid, no other specific nitrogen- or phosphorus-containing end-products of nuclein metabolism occur in appreciable quantities in human urine."

"Uric acid excretion normally is dependent only upon diet."

Mochizuki (1901) judged from an increase of nitrogen, uric acid and phosphorus in the urine that the proteins of a thymus broth were readily absorbed through the colon when introduced *per rectum*.

Sweet and Levene (1907) studied nuclein metabolism in a dog with an Eck fistula, that is, an anastomosis between the portal vein and the inferior vena cava, an operation which cuts off the activity of the liver in oxidizing uric acid to urea. The experiments were made in three-day periods after several weeks' feeding on the purin-free diet which was used as the basal ration in the experimental periods. Observations were made (1) with the purin-free diet, (2) on a diet containing the same amount of nitrogen but partly in the form of nucleoprotein, adenin sulphate, sodium nucleate or thymin; also (3) on a diet of adequate calorific value, but low in nitrogen, and finally, (4) when no food was taken. The purin-free diet was composed of plasmon, cracker dust and lard; and the low-protein diet was composed of cane sugar, cracker dust and lard.

Nitrogen equilibrium was maintained on the non-purin diet, the uric acid output being higher than normal. Nucleoprotein feeding slightly increased the uric acid output. When 1.0 gm. adenin was fed there was an increase in uric acid corresponding to 44 percent of the base given. Ten grams of sodium nucleate increased the uric acid by more than 40 percent of the purin given, the phosphorus outgo also showing increase. Thymin was eliminated mostly as such. Thymin was not observed in the urine on either nuclein-free or nucleic acid diets. Nucleic acid, therefore, is not completely disintegrated, or its decomposition products are slowly formed, in small quantities, and immediately destroyed. An increased uric acid outgo on the low-protein diet indicated increased cell katabolism, and a

subsequent decreased output showed an adjustment of the metabolism to the continued low-protein diet, this elimination being but slightly increased in the starvation period following.

Abderhalden, London and Schittenhelm (1909) also made use of an Eck fistula in a dog in studying the influence of the liver in nuclein metabolism. From urine observations in connection with nucleic acid feeding it was concluded that the digestion, desamidization and oxidation of the nucleic acid proceeded nearly as usual; the uric acid was not transformed into allantoin to quite the extent that Schittenhelm had found usual with normal dogs. Both uric acid and phosphorus in the urine rose when the sodium nucleate (and starch) was added to a bread and milk diet.

In another experiment with dogs (Schittenhelm, 1909a) sodium nucleate was either fed, or introduced with a probang, (and in one case intravenously) and the urine and feces were examined. Observations of this kind were made with normal dogs, starved dogs, and dogs under the influence of alcohol. The nitrogen elimination indicated that the nucleic acid when introduced by the mouth, was completely absorbed, and then its purins were almost wholly eliminated as allantoin, though all the forms of purin nitrogen in the urine were appreciably increased. Injected salt was not eliminated in the same way as that fed; the nitrogen eliminated was increased by an amount much more than that added, and considerably more of it was in the form of purin bases. Vomiting sometimes followed the introduction by probang. The influence of the chronic alcoholism was evident in a delayed elimination, probably delayed metabolism of the nucleic acid, purins showing in the allantoin output, just as in human alcohol experiments uric acid elimination is delayed. Purin excretion observations were made by Schittenhelm and Bendix (1904, 1905) after feeding or injecting nucleic acid in rabbits.

F. Frank and Schittenhelm (1909) also report nitrogen and phosphorus retention experiments with three human subjects in which, to a constant diet of cereals, milk, eggs, butter and fruit (purin-free) there was added, on the experiment days, 10 grams of the sodium salt of thymus nucleic acid. Determinations were made of total nitrogen, urea,- uric acid-, and purin base-nitrogen, as shown in the table. Patient III had a stricture of the oesophagus and was fed by stomach fistula. The authors concluded that there was a prompt working over of the nucleic acid, with quantitative elimination of the end-products after only one day. The purin bases of the nucleic acid appeared mainly in the form of urea, but little as uric acid, and but a very small part as purin bases.

AVERAGE DAILY PHOSPHORUS ELIMINATION AND THE FORMS OF NITROGEN ELIMINATION FROM NUCLEIC ACID IN MAN

Frank and Schittenhelm (1909)—Grams

Experiment and period	Length of period Days	Body weight of subject Kg.	Food			Urine					Feces		
			Total N	Nucleic acid		Total N	Urea N	Uric acid N	Purin base N	P_2O_5	Total N	Purin base N	P_2O_5
				Purin base N	P_2O_5								
I Fore period..	4	66.1	13.6	.....	...	10.04	8.50	0.109	0.014	2.46	2.3	0.104	1.42
Exp. period..	5	66.0	14.65	0.608	1.4	11.02	9.49	0.140	0.014	2.86	2.43	0.127	2.60
After period...	3	66.1	13.6	.....	...	10.15	8.86	0.121	0.011	2.32	2.19	0.107	1.37
II Fore period...	4	45.2	15.35 [1]	.....	...	11.20	9.76	0.092	0.011	2.27	2.38	0.158	2.879
Exp. period.	4	45 8	16.40	0.608	1.4	12.36	10.88	0.156	0.015	2 59	1.88	0.204	3.659
After period...	4	46.2	15.35	.....	...	11.42	10.32	0 098	0.008	2.47	1.76	0.131	3.00
III Fore period..	3	25.8	8.17	.....	...	6.55	5.60	0.063	0.005	1.33	0.42	0.0064	1.34
Exp. period..	2	25.3	9.22	0.608	1.4	6.57	5.733	0.267	0.014	2.202	0.528	0.0325	1.69
After period...	3	25.6	9.34	.....	...	6.05	5.15	0.097	0.007	1.458	0.441	0.0061	1.105

[1] One day of this period only 13.80 gm.

This finding of urea as the chief end-product of the purin nitrogen of nucleic acid in man is not in harmony with the view held by many that uric acid must be the end-product because in man no uricase is found. Dohrn (1913) reports one experiment in which the urea was not uniformly increased by nucleic acid intake. In his observations both nitrogen and phosphoric acid elimination were increased beyond the intake.

Marfori (1908b) notes that, by administration of nucleins, not only all the phosphorus of the nuclein appears in the urine, but an excretion greater than corresponds to the same. The mass of the phosphorus found in the feces is increased. Nuclein or nucleic acid given by mouth to dogs is absorbed, and excreted in the urine in the form of phosphates. Nucleoproteins are consequently not in condition to offer assimilable phosphorus to the organism. This observation is not in accord with prevailing opinion.

Oeri (1909), from a brief experiment on himself, aged 27, concluded that the phosphorus of nucleate is set free in the form of phosphoric acid in the intestine, and that the path of its elimination is then determined largely by the presence or absence of calcium. If calcium is present, calcium phosphate forms and is excreted by the intestine; but if calcium is not available, the phosphoric acid is excreted by the kidneys. The nucleate was taken in a single dose of 12.99 gm. of the sodium salt; conditions, therefore, were not favorable to observations on nitrogen and phosphorus retention from nuclein.

Sokolov (1912) is said to show that sodium nucleate is not assimilated by the aged, but that its assimilation is marked in young individuals.

From a study of nuclein metabolism in a pig, a part of the results of Schittenhelm (1910) are as follows:

AVERAGE DAILY NITROGEN AND PHOSPHORUS BALANCES WITH A PIG, AS AFFECTED BY NUCLEIC ACID—Grams

Length of period in days	Food	Food	Urine					Feces			Ration.
	N	P_2O_5	N	Uric acid N	Purin N	Allantoin N	P_2O_5	N	Purin N	P_2O_5	
5	8.7	3.80	5.84	0.005	0.016	0 236	1.20	0.265	0.002	0.39	1500 cc. milk.
3	9 49	4.40	6.57	0.009	0.029	0.575	1 63	0.682	0.011	0.695	Same plus 20 gm. nucleic acid from yeast.
3	8.7	3.80	6.30	0.009	0.018	0.255	1.23	0.193	0 009	0.191	1500 cc. milk.
5	14.07	5.30	5.20	0.006	0.027	0.278	1.07	0.550	0.037	0.45	1500 cc. milk; 300 gm. wheat flour.
5	16.12	7.65	6.38	0.016	0.054	0 973	3.32	0.210	0.011	0.20	Same plus 14 gm. yeast nucleic acid.
5	14.07	5.30	6.40	0.009	0.025	0.374	....	0.295	0.016	0.31	1500 gm. milk; 300 gm. wheat flour.

In the first experiment the pig was 8 weeks old; in the second, 4 months old. In the first there was no gain in weight; in the second the pig increased in weight from 25.4 to 31.6 kg., or 413 gm. per day. The author concludes that nucleic acid fed to swine is easily absorbed and completely broken down; the purin portion appears as the end-product allantoin, while the intermediate products, uric acid and purin bases, are eliminated as such only in very small part, about 1-5 percent. In the second experiment, and in another in which there was gain in weight, the elimination of nucleic acid was not quantitative, which indicates that the nucleic acid of the food can be retained and utilized. In other experiments the author showed that allantoin, either fed or injected, was excreted unchanged.

Meier's (1910) work also shows that in hogs nucleic acid is largely absorbed, and the purin fraction appears as allantoin in the urine, with only small amounts of uric acid and purin bases.

Levene and Medigreceanu (1911a), after pointing out some of the difficulties and uncertainties in most of the previous attempts to learn of the exact processes and paths by which nucleins are transformed to the end-products uric acid, allantoin and urea, report data of their own, obtained from a dog, to which were fed various products from the partial breaking down of the acid, as well as nucleic acid itself. An attempt was made to maintain the animal in nitrogenous equilibrium between experiments. No new experiments were performed before the animal returned to its normal condition. The substances employed were allantoin, hypoxanthin, inosin, nucleic acid, and thymus gland. The urine was analyzed for the following substances; total nitrogen, uric acid, purin bases, ammonia, amino nitrogen and allantoin. Percentage transformation of the fed purin was calculated on the basis of nitrogen eliminated in the feeding experiments in excess of the nitrogen output in the normal periods.

The authors conclude that the urinary constituents derived during 24 hours from the purin nitrogen of the nucleic acid administered were 85 percent allantoin and 15 percent urea; and that the urinary constituents excreted in 24 hours from the purin nitrogen of thymus were 17 percent allantoin, 5 percent uric acid and 78 percent urea. There was no increase in the amino nitrogen output after any one of these experiments.

"From the results of these experiments it is apparent that the highest proportion of allantoin output follows the administration of nucleic acid and of hypoxanthin; the proportion is lower after the

administration of inosin. Thus it seems possible that the first step in the disintegration of nucleic acid in the organism is the liberation of purins and not of inosin."

London (1909) has presented unique evidence as to the nature and extent of digestion in the several portions of the alimentary tract. These several regions were studied independently, by means of fistulae, at various points in the intestine. Experiments were conducted on four dogs with nucleoprotein from horse liver. London concluded that about two-thirds of the nucleoprotein goes into solution in the stomach, but with the splitting off of only 2-3 percent of the phosphorus, the dissolved substance giving the reactions of nucleic acid. In the intestine nucleic acid is decomposed, the principal part in the digestive process being played by the intestinal secretion.

By further use of London's fistula method, London and Schittenhelm (1910) watched the digestion of nucleic acids in dogs having fistulae in the duodenum, the jejunum, the ileum or the ileo-coecal region. In one series of experiments the dogs were fed milk, white bread and the sodium salt of yeast nucleic acid; in two other series, white bread and the sodium salt of thymus nucleic acid; in a fourth, the sodium salt of thymus nucleic acid with water only; and in a fifth—a control experiment—they were fed bread and milk only. From this work it appears that nucleic acids are neither changed nor absorbed in the stomach; but in the intestine there is a change by which a small part seems to be split, with the formation of free purin bases, while a larger part is so changed that dialyzable cleavage products are produced which still contain organically combined purin bases. To determine whether the digestion katabolism corresponds with the hydrolytic cleavage which Levene has observed, Levene's method of fractioning the lead acetate solution was followed, and in that way it was shown that a change does take place by which the amount of unaltered nucleic acid becomes less the nearer the fistula is to the lower ileum, and products are formed which are rich in purin bases. According to Levene's interpretation, these might be either a nucleoside (e. g., guanosin), or a mononucleotide (e. g., guanylic acid), or a mixture of the two.

The absorption of nucleic acid or its cleavage products is found to take place mainly in the lower parts of the intestine, the lower jejunum and the ileum, as indicated by these cleavages observed. Since the amount of free bases found among these digestion products is very small, it would appear that complete cleavage is not necessary for absorption. The control experiment showed that the body does not give off any purin bases in the digestive juices, as has repeatedly been affirmed.

Later communications from these authors (London, Schittenhelm and Wiener, 1911,1912) show that undoubtedly guanosin is among the cleavage products formed in the intestine, and probably also guanylic acid and adenosin, and that the active agent in the process is not the pancreatic juice, but the intestinal juice. This last point is learned both from artificial digestions with the juices, and from observations, by the fistula method, in which the normal dog was compared with (1) a dog having no stomach, (2) a dog with the pancreatic juice shut off from the intestine, and (3) a dog without a pancreas.

From this series of investigations, then, we are given the following understanding of the digestion of nucleic acids: If a polynucleic acid be ingested, it undergoes little or no digestion or absorption in the stomach; but in the intestine the intestinal juice first breaks it into mononucleotides, without splitting off any phosphoric acid, and then the phosphoric acid splits off from the mononucleotide, forming a mononucleoside, which is a combination of purin base or pyrimidin base and carbohydrate. This process takes place during passage through the small intestine, the products apparently being absorbed in states of incomplete cleavage. The various organs and tissues of the body apparently have the power to cleave further and to transform the purin complexes.

Mayesima (1913) found that a dog with the anterior 90 percent of the small intestine removed was able efficiently to absorb the nitrogen and phosphorus of yeast nucleic acid. Assuming that the normal region of absorption of nucleic acid is the lower part of the small intestine emphasis might be put, in the interpretation of this observation, on the activity of the remaining 10 percent of the small intestine or on a compensatory absorptive activity of the large intestine.

ACCOMPANIMENTS OF THE INGESTION OR INJECTION OF NUCLEAR MATERIAL

High Purin Excretion. For considerations of the amount and origin of the uric acid of the urine, especially as related to nucleins, see the extensive discussions and reviews of literature the citations to which follow:

Burián and Schur (1900, 1901, 1903); Wiener: Die Harnsäure; Ergebnisse der Physiol. I (1902), Abt. I; Mendel, L. B. (1906); Brugsch and Schittenhelm (1907a, b, c, d, e, f, 1908-9, 1910) and Brugsch (1909).

Briefer discussions or reports of experimental evidence bearing on this question, which have come into this research are the following:

Salomon, 1878; A. Kossel, 1882; Horbaczewski, 1889, 1891a, 1891b, 1893; Weintraud, 1895a, 1895b, 1900; Kuehnau, 1895; Hess and Schmoll, 1896; Mayer, Paul, 1896; Camerer, W., Sr., 1896; Umber, 1896; Jerome, 1897-8, 1899; Milroy and Malcolm, 1898; Minkowski, 1898; Loewi, 1900, 1900-01; Kaufmann and Mohr, 1902; Mendel, L. B., Underhill and White, 1903; Schittenhelm and Bendix, 1904, 1905; Folin, 1905; Macleod and Haskins, 1906; Sweet and Levene, 1907; Schittenhelm, 1907; Brugsch, 1908; Abderhalden, London and Schittenhelm, 1909; Schittenhelm and Wiener, 1909; Scaffidi, 1909b; F. Frank and Schittenhelm, 1909; Schittenhelm, 1909a, 1910; Meier, 1910; Fromherz, 1911; Smetánka, 1911; Levene and Medigreceanu, 1911a.

Horbaczewski (1889, 1891a, 1891b, 1893) first showed that the action of blood on pulp of spleen, and of several other organs, results in a formation of uric acid, and he held that normally uric acid formation in mammalia is due to the action of living blood on the lymphatic elements, particularly the leucocytes. He considered the various causes which increase the uric acid of the urine, including nuclein ingestion, and noted that nearly every one is accompanied also by high leucocytosis; and it was his idea that the increased uric acid came as an indirect effect of these agents, they bringing about a high production of leucocytes which must be followed by much destruction of leucocytes, and the elimination of their purins in that form.

A. Kossel (1882) suggested that there might naturally be connection between the nucleins and uric acid output, and it is now generally recognized that nucleins of the food contribute directly to the purins of the urine; and accordingly the urinary purin is spoken of as including two portions; endogenous purins, arising from the leucocytes and from the nuclei of tissue cells, and exogenous purins, arising from nuclear material introduced into the body. The attempts of Burián and Schur to differentiate these two portions, to determine the amounts due to each, and to establish some laws governing one or the other factor, have had considerable influence on the later thought.

Burián and Schur (1900, 1901, 1903) compute the endogenous urinary purins as the amount eliminated on a diet which supplies the nitrogen requirement but which is practically free from purins. The amount so determined is used also as a measure of the exogenous purins from a diet containing purins, Burián and Schur holding that the endogenous purin maintains a constant value for the same individual under the same conditions of living, but that it differs for different individuals. On this basis the exogenous purins are considered as originating entirely from such bodies contained in the food; and that portion of the food purins which appears as uric acid in the urine is, for human subjects, dependent on the nature of the food rather than upon individual variation. "Factors" are de-

veloped for different species, by which the amount of uric acid eliminated during 24 hours may be multiplied to make an approximate determination of that present in the blood. Some of the factors given are, for man, 2; for rabbit, 6; for carnivora, 20-30.

Some of the observers do not agree with Burián and Schur as to the constancy of endogenous purin for the same individual, or as to the independence of the exogenous purin of personal variation.

It must be remembered that in this relation purin includes all the alloxuric bodies as well as uric acid, that is, all those compounds constructed with the group C_5N_4 as a nucleus. Both base and acid are increased in human urine by nuclein in the food. In dogs, cats, pigs and some other animals the increase appears mostly as allantoin.

The endogenous purin may be increased by whatever body processes are accompanied by a great tearing down of nucleated cells, such, for example, as excessive strain on the digestive organs, and the destruction of cellular tissue in disease or on too low protein intake.

Smetánka (1911) finds that any protein, even if purin-free, leads to increased uric acid excretion, a fact which he attributes to changes in the composition of the cells of the digestive glands during their activity. Ingestion of polysaccharides causes less increase, corresponding with less activity of digestion called for. Honey, however, causes great increase, which may be explained by the intense activity of the liver cells in forming glycogen. Increase of total nitrogen metabolism does not in itself increase uric acid excretion.

Schittenhelm and Seisser (1911) conducted feeding and intravenous injection experiments with dogs and rabbits showing that sodium thymonucleate influences but slightly the outgo of uric acid and purin bases, while it prominently increases the outgo of allantoin; from which they conclude that nucleic acid is without influence on uric acid transformation, especially that it cannot protect uric acid from further decomposition.

In the observations of M. Tschernoruzki (1912) with dogs, both nitrogen and phosphorus excretion, after the administration of the sodium salt of nucleic acid (Merck's), indicated an increased metabolism of phosphorized body tissues.

The behavior of iron-iodine-paranucleate (iodtriferrin), when fed to dogs and rabbits, has also been studied by Salkowski (1913a).

Hyperleucocytosis. As a constant accompaniment of the taking of nuclein-rich food, and especially of the injection of nuclein or

nucleic acid, and closely associated with increased uric acid elimination, is an increase in the number of leucocytes in the blood. The high phosphorus output at the time of such nuclein intake has been attributed to a leucocyte destruction following the great leucocyte formation. Since leucocytes are so effective in battling with pathogenic bacteria, use has been made of nuclein injection as a prophylactic measure in guarding against infection in preparation for surgical operations.

In 1891 Horbaczewski called attention to this accompaniment of nuclein feeding, and in 1892 summed up the results of his experiments thus (we quote through Schaumann): "The only observed symptom of nuclein action which is constant in normal animals and men is an increase of leucocytes in the blood, which may reach as high as 100 percent. This leucocytosis appears soon after nuclein is given, decreases gradually, and may entirely disappear after 18-24 hours. The nuclein leucocytosis appears constant also in different pathological conditions."

Schaumann also says that, "Goldscheider and Jacob (Zeit. f. klin. Med., 25, 1894) had somewhat different results in their experiments on these phenomena. They used carbolic-glycerin extracts of different organs, which they applied by injection. In these cases no changes in the blood were caused by the extracts from pancreas, liver, kidneys, or thyroid gland, while those of spleen, bone marrow and thymus gave positive effects, though differing. The last two produced a pronounced influence in the direction of hypoleucocytosis, while the spleen extract injection caused a hyperleucocytosis, the intensity and duration of which were several times as great as with the giving of spleen pulp *per os.*"

From among the many other observations on leucocytosis the following may be of interest. Some have asserted that the increase of leucocytes is only an apparent increase due to a transfer of these corpuscles from the central circulation to the peripheral. Delano Ames and A. A. Huntley (1897) disproved this theory by their experiments on dogs. Comparison was also made of the respective numbers of the three varieties of leucocytes, which are supposed to be three stages in their development—small mononuclear, large mononuclear, and polynuclear cells. It was noticed that the administration of ether produced an increase, the extent of which seemed to depend on the amount of ether used. "2. Before the administration of nuclein the counts showed that the number of leucocytes in the peripheral and in the central circulation was practically the same.....3. Following the administration of the nuclein solution there was immediately, that is by the end of five or

ten minutes, a noticeable increase in the number of leucocytes in both the central and peripheral circulation. 4. At this time the percentage increase was most marked in the young, mononuclear forms .....while the proportion of polynuclear elements was proportionately low. 5. The longer after the injection of nuclein the greater was the actual increase and the number seemed steadily to rise in both the peripheral and central circulation."

According to Schittenhelm and Bendix (1905), yeast nucleic acid, and α-thymus nucleic acid injected in rabbits as the sodium salt, both caused at once hypoleucocytosis, followed in 6-8 hours by great hyperleucocytosis, which corresponds with Renner's observations (See p. 258). According to Schaumann, Walter Hannes observed as high as 144 percent increase of leucocytes. Renner's greatest increase was even higher, 452 percent.

Meisen (1909, 1911) finds that nucleic acid, subcutaneously injected in growing dogs, produces hyperleucocytosis, without injurious accompaniments; that the relative number of mononuclear neutrophiles is not increased; that with repeated injections there is an up-and-down variation in the number of red blood corpuscles and in the haemoglobin content; and that injections kept up for a long time cause a greater firmness in growing bones.

Kaupp (1911) reports certain blood observations on horses after nuclein injections, the conclusions from which may be summed up thus: Nuclein increases the number of leucocytes in the blood, the number of polymorphonuclear leucocytes, and the power of phagocytosis of the individual leucocyte. Nuclein decreases the time of coagulation of the blood. To obtain the best results in cases of infectious diseases, nuclein should be given hypodermically. To obtain desirable results in cases of hemorrhage, the nuclein should be given intravenously.

M. Tschernoruzki (1912) made a special study of the effects of introduction of the sodium salt of nucleic acid in dogs. The dogs receiving the nucleate either *per os*, subcutaneously, intraperitoneally or intravenously showed a more or less marked hyperleucocytosis, and a somewhat larger number of red corpuscles than an untreated dog. As judged from the number of leucocytes found, the strongest hyperleucocytosis resulted in the case of intravenous injection (353.3 percent of the value in the control dog), next in the case of subcutaneous administration (204.8 percent), then intraperitoneal introduction (187.6 percent) and last, in the case of introduction *per os* (162.5 percent). The animals quickly acquired a certain immunity to considerable quantities of the nucleate.

Timoshok (1912) studied the influence of sodium nucleinate (from yeast) on rabbits infected with *Staphylococcus pyog. aur.* The nucleinate caused a rapid polynuclear hyperleucocytosis, and alteration of enzyme functions, the latter varying either directly or inversely as the changes occurring in *Staphylococcus* infection without sodium nucleinate. There were noted: (1) Parallel increase in lipolytic and catalytic activity of the organs; (2) parallel decrease in the sugar-synthesizing energy of the organs, and the diastatic and catalytic energy of the blood; (3) increase in the lipolytic power of the serum (a decrease occurred in the absence of sodium nucleinate); (4) decrease in the diastatic and sugar-synthesizing energy of the organs, and the anti-trypsin content of the serum (an increase occurred when sodium nucleinate was absent).

MISCELLANEOUS EFFECTS OF NUCLEAR MATERIAL

Milroy and Malcolm (1899) reported a histological study with rabbits and guinea pigs which was concerned with the intracellular wanderings of granulated leucocytes under the influence of nucleic acid, thymic acid, adenin, guanin, cytosin and metaphosphoric acid.

Bang (1901b) tried the effects of injection of guanylic acid and of β-nucleoprotein with dogs. Both of these compounds greatly reduced the rate of coagulation of blood, the nucleoprotein most markedly. Blood pressure fell off noticeably after the injection. Immediately after the injections the dogs were always restless, and breathed irregularly and quickly; then the excitement passed and was followed by partial narcosis for some minutes. In the case of guanylic acid injection, the urine became alkaline about half an hour after injection. After 24-48 hours it was again acid. There was no more ammonia present than normal, and the alkaline reaction could not be explained. Albumin was present to the extent of 1-3 parts per thousand, which, it was thought, might be due to the lowering of blood pressure or to the acid having toxic action on the kidneys.

Galeotti (1900) reports tests of the effects of bringing nucleoproteins extracted from animal tissues or from bacteria, into contact with different animal organs or self-moving cells. The report is that nucleoproteins exercise considerable influence on protoplasm in general, the results of the influence varying according to the cells concerned. For some cells the influence was of the nature of excitement, and for some it was paralyzing.

Mendel, Underhill and White (1903) report experimental studies of the physiological effects of nucleic acid, particularly that from wheat embryo, tritico-nucleic acid. Observations of the following kinds are reported:

(1) Manometer tracings of blood pressure after intravenous injections, (2) coagulation time of blood taken from femoral vein after injections, (3) coagulability, composition and rate of flow of lymph from thoracic duct, (4) immunity effects, (5) urine examination after feeding, and intravenous, intraperitoneal, subcutaneous and rectal injection, (6) urine and feces examination and leucocyte count after feeding and rectal injection.

The authors' concluding summary is:

"The more important observations recorded in this paper indicate that the vegetable nucleic acid obtained from the wheat embryo resembles, in its physiological effects, the guanylic acid of the pancreas. Introduced in sufficient doses into the circulation, it may produce a fall in arterial pressure; a change in the coagulability of the blood; an increase in the flow of lymph and a change in its composition; and perhaps, also, a degree of immunity toward subsequent injections.

"The ingestion of nucleic acid is followed in man by an increased output of uric acid, and in the dog by the excretion of allantoin. These products correspond in either case to only a portion of the purin radicals introduced. In animals allantoin excretion was also observed after the introduction of vegetable nucleic acids into the body per rectum, intravenously, intraperitoneally, and subcutaneously. Some features of intermediary purin-metabolism are discussed."

Guerrini (1903) made injections of 1 percent aqueous or sodium carbonate solutions of nucleoproteins from the liver and brain of white mice and of dogs into the peritoneal cavity of dogs and white mice, following with histological examination of the organs of the animals after different intervals of time, varying from one-half hour to 72 hours. Both excitations and degenerations were always found to have taken place in the parenchymatous cells of the livers and of the kidneys, the intensity and the time of appearance of the changes being in evident relation to the quantity of nucleoprotein injected. Both kinds of changes were evident in both the nuclei and the cytoplasm of the affected cells.

Enea (1903) carried out injection experiments with rabbits, from which he concluded that nuclein extracted from pathogenic and non-pathogenic bacteria has a toxic action; that in maximum doses it causes immediate death by destruction of leucocytes and coagulation of the blood, while in lesser doses it produces gradual progressive destruction of leucocytes, but not general coagulation, death occurring after different lengths of time that are proportional to the quantities of nuclein injected. It also increases the normal bactericidal power of blood serum, the effect not being specific for the organism from which the nuclein was taken.

Schittenhelm and Bendix (1904) found gelatinizing, unabsorbed nucleic acid in the urine of rabbits after the subcutaneous injection of the sodium salt of α-thymonucleic acid; and the same acid injected in the ear vein of rabbits led to the appearance of red and white corpuscles, nucleic acid cylinders, and the unchanged nucleate in the urine; also purin bases were present; the kidneys were disturbed. Addition of uric acid to the nucleate injected made little difference, save that uric acid was included in the nucleic acid cylinders.

Desgrez and Zaky (1904a, 1904b, 1904c, 1905) concluded that in guinea pigs and dogs the nuclein of yeast, or its nucleic acid, favored retention, especially of proteins, and a mineralization of the skeleton. (See Growth and Comp. of An. as Aff. by Comp. of Glyc.)

Snowman (1905) mentions an experiment of Miyake, reported in Med. Annual for 1905, in which the injection of 1 c.c. of 0.5 percent solution of nucleic acid into the peritoneum of a guinea pig caused the animal to resist a subsequent inoculation with *Bacillus coli* of 20 times the normal minimum fatal dose.

Pouchet and Chevalier (1906) report that injection of nucleic acid (from pancreas and from fish roe) causes an increase of leucocytes. An intravenous injection of 0.004 gm. per kilogram body weight in dogs causes acceleration of heart beat. With a larger dose (0.020 gm. per kilo.) an irritating action is produced upon the endocardium, and there is a decrease in blood pressure, and a slower rate of heart beat. After a certain time the original blood pressure is regained, and the heart beat becomes normal. The effects are thought to be due to action on the central nervous system.

Knapp (1908) states, after his experiments with rats, that continued use of sodium nucleate causes nephritis and fatty degeneration of the liver.

Achard and Redfield (1911) used a nuclein solution as a wound dressing and consider that it promoted healing. Much literature that we have not seen, on the bactericidal effect of nucleins, is reviewed.

M. Tschernoruzki (1911, 1912, also Czernoruzky, 1912) has recently reported an interesting study on the action of nucleic acids on the fermentative processes of the animal organism. Thinking that the resistance which the organism acquires against infection from the use of sodium salts of nucleic acids is not due to leucocytosis alone, because it differs from the effect of aleuronate, which produces equally great leucocytosis, but may be in part due to alterations of the fermentative functions of the organs, he put to test the individual organs of dogs, after long periods of ingestion or injection of nucleic acid.

Five young poodles of the same litter were used. One was kept as a control, and the other four received Merck's sodium nucleate, from yeast: No. 1 intravenously, No. 2 intraperitoneally, No. 3 subcutaneously, and No. 4 by mouth. Treatment was begun at about the second month and continued 4½-5½ months, with increasing doses up to 1.5 gm. per kilogram of body weight. Rise of temperature and leucocytosis, as results of the treatments, were noted. All of the dogs were killed and the organs removed, ground, dried, extracted with physiological salt solution, and the extract tested for ferments. The organs examined were; liver, lungs, spleen, brain, kidneys, muscles and thymus; and the following were the tests applied:

Ferments tested for	Tests
Protease (Tryptase)	Amount of extract required to digest completely 0.5 c.c. casein solution
Amylase	Amount of extract required for digestion of starch to disappearance of iodine reaction
Diastase (Dextrinase)	Amount of sugar produced from starch
Catalase	Potassium permanganate method (Results are not reported because conditions of preparation of organ extract would vitiate results)
Nuclease	Inorganic phosphorus produced from nucleic acid in 48 hrs. at 37.5°C.
Lipase	Acid split off from 1 percent monobutyrate solution
Lecithase	Acid split from 2 percent lecithin emulsion (All results here were negative.)

The author's conclusions are in part as follows:

Introduction of nucleic acid into the animal organism has a marked influence on its fermentative activities. As to the significance of the manner of its introduction—the least effect on fermentative functions was observed with subcutaneous and the greatest with intravenous injection. As to the ferment—the greatest changes were found with the amylolytic ferment. With regard to the organs—the greatest variations in the sense of increase of fermentative energy were in the brain, the lungs, the muscles and the thymus. In the brain the value for amylase was 400 times as high as the normal, for diastase 4.4 times, and for protease 10 times. In the lungs the value for amylase was increased 250 times, in the muscles—for amylase 6.4 times, in thymus—for lipase 2.5 times. The brain considerably exceeded the other organs in the number of ferments evident, as well as in the amount of change in their action. Merck's sodium salt of yeast nucleic acid produced no evil effects in the animal organism under continual use of large doses, and with different ways of introduction. Perhaps the therapeutic significance of nucleic acid preparations in various diseases finds some explanation in the facts here reported. Especially in progressive paralysis, the benefit may be due to changes in the fermentative functions of the brain. The strengthening of the neucleolytic function in the blood was greatest in the polynuclear white corpuscles. Of the organs examined, there seemed to be great increase

of nuclease content in the thymus, pancreas and liver, less of an increase in bone-marrow and spleen, and decrease, or but slight increase, in brain, lungs, kidneys and muscles. The dog which received the nucleate by mouth showed the greatest nuclease variation from normal, considering all the organs together; and the one receiving it subcutaneously, the least.

In addition to these effects on ferments, and to a hyperleucocytosis and increased purin metabolism, Tschernoruzki (1912) noted in the dogs a rise in body temperature and certain derangements in general condition, whatever the method of introduction. In the case of parenteral injection, doses which approached the value of 1 gm. per kg. of body weight produced rather marked disturbances, such as loss of appetite, apathy, etc. After a dose of 1.5 gm. per kg. of body weight the intravenously injected dog showed symptoms like those of poisoning, but the dog receiving it by way of mouth showed no disturbance of general condition, with the exception of diarrhoea.

At the close of this second paper Tschernoruzki's conclusions were as follows: There is a strong analogy in the action upon the organism of nucleic acid, and infection. Both result in hyperleucocytosis, rise in temperature, disturbance of general condition, and increase of metabolism; and both react upon the fermentative processes, and bring about a certain degree of immunity. Nucleic acid is then apparently an agent which stimulates the natural protective agencies of the organism, especially the leucocyte function. This explains the therapeutic significance of nucleic acid and gives basis for its use in medicine. His final conclusion is that "by introduction of nucleic acid into the animal organism the nucleolytic function of the latter is increased."

Brossa (1912) made an attempt to determine what he calls the biological value of α-nucleic acid of thymus, for a dog and for hens, by applying to the nitrogen intake and output the following formula, which he attributes to Thomas:

$$\frac{d-[c-(a-b)]}{a-b} \cdot 100$$

A nitrogen-free diet was fed for a brief time, followed by a like diet with sodium nucleate added, and to the data obtained the formula was applied by letting "a" equal the nitrogen taken in the food, "b" that excreted in the feces, "c" that in the urine on the nitrogen-containing food, and "d" that in the urine on the nitrogen-free diet. In this way it is calculated that the biological value of the nucleic acid for the dog is 60 percent, and for the hens 80 percent.

Goubau and VanGoethem (1913) determined by intravenous injection experiments with dogs that the effects, on the circulation, of injecting nuclein, and nucleohistone are quite comparable with those of proteins in general. The primary effect is thromboplastic, and is followed by a more lasting antithrombic influence. Nucleins paralyze, slightly, the motor center of the heart immediately after the injection, with an enormous increase in the frequency of the beats, followed by a secondary enfeebling of the beats.

See also Bókay (1877), Gumlich (1894), Jacob and Bergell (1898), A. Neumann (1898).

SIGNIFICANCE OF NUCLEOPROTEINS AND NUCLEIC ACIDS AS ACTIVE AGENTS IN SPECIFIC BODY PROCESSES

From the mere fact of the presence of nucleoproteins at the heart of every cell, it may be inferred that they are of great importance in the life and the activity of cells, as Kossel has repeatedly remarked. As to just what is their part we cannot say, but we may quote Gustav Mann as to one probability. As a result of his extensive study and observation, chemical and microscopical, he says (Chemistry of Proteids, 1906, p. 454):

"What we call life is simply the manifestation of special chemical compounds, and if we see microscopically that every manifestation of metabolism is accompanied by enormous changes in the nucleoproteids, and that the rapidity with which nucleoproteids or the nuclear basophil chromatin reacts to food substances is directly proportional to the ease with which the food is absorbed, we cannot arrive at any other conclusion but that the nucleoproteids are the agencies by which amino-acids are built up into the cell plasm."

Herlitzka and Borrino (1902a, 1902b, 1903), following Bottazzi, attribute catalytic actions to the nucleohistone of cell nuclei and the nucleoprotein of the cytoplasm. They tested the isolated nucleohistones and nucleoproteins of liver, thymus and kidney as to their power to decompose carbonates, and to free the CO_2 (the power was possessed by both), to break down haemoglobin (possessed by both kinds of compounds, but only those of liver), to form urea (possessed by neither), and to digest sugars (most action by compounds from kidney, especially from its nuclei).

Fibrin ferment and blood coagulation action have been ascribed to nucleoproteins and nucleohistones of blood and of muscle. The injection of nuclear matter from various sources has been followed by intravascular coagulation. (See Halliburton, 1892; Halliburton and Brodie, 1894; Pekelharing, 1895, 1896; Lilienfeld, 1895; Huiskamp, 1901a). Other substances, however, introduced in this way

have also led to such consequences. It is Pekelharing's (1895,1896, 1914) idea that the fibrin-ferment, thrombin, forms from a nucleoprotein of the blood or organ, it being perhaps a calcium compound of the nucleoprotein.

On the other hand, several observations which have been quoted above show that injections of nucleic acids affect the blood in such manner that its coagulation is considerably retarded. Doyon and his associates (Doyon, 1912; Doyon and Dubrulle, 1912; Doyon and Sarvonat, 1912a, 1912b, 1912c, 1913a, 1913b, 1913c, 1913d, 1913e, 1913f; Doyon, Dubrulle and Sarvonat, 1912, and others) have reported investigations of this power *in vitro*. Anticoagulating bodies were extracted from liver, testicles, intestine, thymus, pancreas, mesenteric ganglia, beer-yeast, blood corpuscles of birds, and haematogen of egg. Most of these were nucleic acids or nucleoproteins; and it is held that a phosphorized nucleus is essential to the anticoagulating power. The degree of effect of nucleic acid was compared (Doyon and Sarvonat, 1913c) with that of ortho-, pyro- and meta-phosphoric acids, with the resulting observation that orthophosphate does not, under the conditions used, exercise any sensible anticoagulating action, while the pyro- and meta-phosphates do. The amounts of sodium metaphosphate and sodium nucleate with the same content of phosphorus showed the same degree of anticoagulating action, and these observations are taken as supporting the view that the phosphorus of nucleic acids is present as metaphosphoric acid. Glycerophosphoric acid and lecithin were inactive in corresponding amounts.

Pepsin had been considered by some to be a nucleoprotein, but Pekelharing (1902) showed that the phosphorus content of the preparation may be reduced by purification processes, and that in all probability phosphorus is not a constituent of pure pepsin. Giacosa and Dezani (1909) also report the isolation from pig stomach of a digestive enzyme which is still active when free from phosphorus.

THERAPEUTIC AND PROPHYLACTIC USE OF NUCLEINS AND NUCLEIC ACIDS

Some of the effects of isolated nucleic acids in the diet are beneficial and some otherwise. If the body be in normal condition, they are well used and are favorable to nitrogen and phosphorus retention; and in pathological cases the same is usually, but not always, true. When the amount of uric acid in the system is excessive, nucleins should be avoided. In special cases they may be of decided advantage, especially if injected, because of their effects upon the circulation and upon the number of blood corpuscles, particularly the leucocytes, and upon the power of phagocytosis. They have

been used with apparent benefit in several diseases, and most strikingly as a prophylactic measure before surgical operations and child-birth. See the reviews of Aulde (1900), Martinet (1902b) and Meisen (1911) of the literature of nucleins and nucleic acids from the point of view of therapeutics.

Larned (1902) describes a series of iron, copper, mercury and silver nucleids as reconstructives and tonics, and as possessed with the power to increase physiologic resistance, and functional activity of secretory organs; and Burnet (1903) says that the metals of these salts are better used when administered in this form than in other forms.

Tomlinson (1897) reports that in infantile scrofula, and other cases of enlarged lymphatic glands, with discharges, the stimulation of leucocytosis prevents suppuration, if it has not begun, and increases it, if it has begun, so that a more complete cure is brought about.

Laumonier (1905) also reports as being brought nearer to normal, under his observation, certain more or less definitely established physiological states.

Backus (1907) reports apparent benefit in the cure of mange.

Joseph Hoppe (1907a) made artificial nucleic acid preparations from yeast cells for use with children with nervous disease.

Donath (1909) discusses the benefits from nuclein injection in the treatment of progressive general paralysis. He states that the injection at intervals of 5-7 days of 50-100 c.c. of a 2 percent solution of sodium nucleate, with an equal quantity of sodium chloride added, is effective in the initial stages of this disease. The injections caused a rise of temperature and an increase of leucocytes, with increased oxidation, which brought about a destruction of the poisonous metabolic products formed by the disease.

Bachrach and Bartel (1907) conducted experiments in which yeast nucleic acid, added to protein media containing tubercle bacilli (from man), increased the speed of reduction of their virulence. On the other hand, the addition of yeast nucleic acid to suspensions of the bacilli in distilled water helps to retain the virulence of the organisms, which in distilled water alone become avirulent in but a few days.

Ward (1910) reported favorable results from intravenous injection of sodium tritico-nucleate in physiological salt solution in the treatment of tuberculosis. The anaemia and oxygen-starvation of the tuberculous patients are associated with a low specific gravity of the blood, due to a decrease in the number of red corpuscles, and, at the same time, the appearance of increasing numbers of poikilo-

cytes. It is said that under the influence of the nuclein-saline solution the poikilocytes rapidly disappear from the circulation, the haemoglobin being eliminated by the liver as bilirubin and biliverdin; the deformed cells being replaced by new and healthy erythrocytes more rapidly than is possible under any other form of treatment as yet devised. This author, then, thinks that the administration of nuclein produces its good effects, not chiefly by inducing leucocytosis, but by effecting an upbuilding of erythrocytes and haemoglobin.

Though nucleins and nucleic acids may have bactericidal action in themselves (see Vaughan, Novy and McClintock, 1893; Kossel, H., 1894), their use to prevent infection, in cases of exposure of the tissues to pathogenic bacteria, is probably to be attributed more largely to their leucocytosis-producing power. Renner (1905) reported such use of yeast nucleic acid in 133 surgical cases. Usually 50 c.c. of a 2-percent solution of the acid in sodium chloride solution was injected in the breast within 24 hours before the operation. There was a brief hypoleucocytosis, followed by a pronounced hyperleucocytosis. Apparently the resistance against *Bacterium coli* and other pathogenic bacteria was increased. The increase of leucocyte count amounted to from 9 to 452 percent (with the exception of 3½ percent in one case where the initial count was very high); in 4 cases there was a lowering of leucocyte count, at least temporary, of 9-14 percent; the average increase in 121 cases was 118 percent. For certain undesirable effects to be guarded against see the original.

See also Pollak (1906); Hannes (1906); Anzilotti (1911); Achard and Redfield (1911); also (through Schaumann) v. Mikulicz (Archiv f. klin. Chirurgie 73, Nr. 2), Miyake (Mitteil, aus den Grenzgebieten der Medizin und Chirurgie 13, Nr. 14, 15) and Dudgeon and Ross (Amer. Jour. of the Med. Sciences 1906, 17; Presse médicale 1906, 569).

SUMMARY

Very little is known as to the details of the anabolic processes in the body; but it seems probable, though not proved, that the animal organism is capable of synthetic formation of nucleins and nucleoproteins, even without purins being supplied as such. Observations reported as evidence of such apparent synthesis with inadequate supply of purins are of the following types: The development of the genitalia of fish while no food is taken; the growth of young mammalia when milk is the only article of diet; the transformations within eggs and embryos; and apparently normal growth on experimental purin-free (or low-purin) diet. However, the evidence is not complete on any one of these points.

As to katabolic processes acting on nucleoproteins, nucleins and nucleic acids, tests *in vitro* by isolated enzymes or by fluids taken from the digestive tract indicate that, though proteins may be separated from nucleoproteins, and nucleins or nucleic acids may be dissolved by gastric juice, this juice does not cause cleavage; that by activated pancreatic juice (trypsin) they are more readily dissolved, which solution may be due to transformation of the α-form to the β-form, or the breaking up of polynucleotides into mononucleotides, though there may be slow cleavage of the nucleic acids, but not a complete breaking down such as frees the reducing substance and the purin bases; that intestinal juice cleaves more rapidly, and frees phosphoric acid, but does not break down the glucoside complex of carbohydrate and base; that within the intestinal wall cleavage may be carried to the state of free purins; and that the intestinal bacteria may not only bring about complete cleavage, but may further oxidize and transform the purins.

Tests *in vitro* with blood and organ extracts indicate that cleavage may take place in the plasma of practically all organs such that the phosphoric acid and the purins are freed from the carbohydrate, and that the purins may then be further altered, though the extent of such alteration differs with different organs, with different species, and probably also with different nucleic acids.

Animal experimentation, giving fairly direct evidence as to what actually occurs in the particular animal under the particular conditions of observation, also indicates that, in the stomach, nucleoproteins and nucleic acids are not broken down, but, in large part, go into solution as such; that in the intestine there is some breaking down; that this breaking down cleaves off phosphoric acid from the carbohydrate-base complex, but does not free the purins; and that nucleic acids and their cleavage products are absorbed chiefly from the lower portions of the small intestine (the lower jejunum and the ileum).

We may suppose, then, that nucleins or nucleic acids are in considerable part taken up by the walls of the digestive tract without change, and in part also after partial cleavage, and that cleavage may be carried further within the intestinal walls, or at the place of storage.

The ingestion or injection of nuclein or nucleic acids is followed by an increased purin output from the body, which probably originates in part in the purin component of the nucleic acid introduced, and in part in the nuclear matter of cells which are broken down as a result of the introduction of this substance. The digestion itself may call for cell destruction which produces this nuclear

matter, or the increased formation of leucocytes may be accompanied by an increased destruction of such cells. There is also an increased phosphate elimination.

Another constant accompaniment of the taking of nuclein-rich food is a marked increase in the number of leucocytes in the blood, following a brief period of decrease. The effect is more pronounced when the nucleic acid is injected. It takes place soon after the introduction and lasts for several hours, affecting all the forms of leucocytes. The phagocytic power of the individual leucocytes is also said to be raised. Advantage is taken of this favorable result in the injection of nuclear matter as an aid in combating infection.

The blood shows other effects of nucleic acid injection which are more or less temporary, and more or less variable with the conditions of operation, and with the amount and kind of acid used. There may be an increase in the red corpuscles, a fall in blood pressure, and a change in coagulability. While nuclein injection is said to increase the power to resist bacteria, it seems to be somewhat toxic itself. One author (Tschernoruzki) has noted favorable effects upon the fermentative powers (amylolytic, diastatic, catalytic, nucleolytic and lipolytic) of the organs as a result of the introduction of nucleic acid, either intravenously, intraperitoneally, subcutaneously, or by way of the mouth. This effect may explain some of the favorable results of the therapeutic use of nucleins and nucleic acids.

The specific activities of nucleoproteins in body cells are not determined; but as they are so universally present as the main constituents at the points of most pronounced manifestation of life—the cell nuclei—it cannot be doubted that they are vital, active agents.

METABOLISM OF CASEIN

PRODUCTION OF CASEIN IN THE MILK GLANDS

Nissen (1886) observed nuclear changes in the milk gland during secretion, and suggested that the casein may form by union of nuclein from the nuclei of the epithelial cells with protein from the cytoplasm of the gland cells. Michaelis (1898) added support to this idea by finding an abundance of the epithelial cells free in the lumen of the alveoli during lactation; and Basch (1898, 1903) isolated a nucleic acid from the gland, from which, by allowing this substance to act on an excess of blood serum, he obtained a body having so many of the properties of cow's casein that he felt sure that it was casein. His conclusion was that within the alveoli this nucleic acid from the cell nuclei (freed either by destruction of the cells

or by an active secretion of the cells) combines with transudated serum, thus forming a nucleoalbumin, the casein. His theory seemed to be further supported in that he was unable to obtain purin bases from his nucleic acid, the nucleic acid thus corresponding with the paranucleic character of casein; but the nucleic acid which J. A. Mandel and Levene (1905) isolated from the mammary gland did show purin bases. This tends to discredit Basch's theory, and other evidence against it is contributed by Löbisch's (1906) studies of nuclein-protein compounds and by Borrino's (1910, 1911) finding a nuclease in the mammary glands present only during lactation. This nuclease would indicate a breaking down of nuclein beyond the point of nucleic acid; so that if the phosphorus of such a compound is used in the synthesis of casein it is by previous destruction of the acid.

There may be significance in the coincidence that a nucleoprotein which Mandel has obtained from mammary glands yields hydrolytic cleavage products in approximately the same proportions as those formed from casein.

Certain experiments reported in 1908 by Michaelis and Rona (1908) imply a relation of the formation of casein to the phenomenon of milk-secretion, the significance of which has not been explained. Subcutaneous injection of casein into guinea pigs and dogs was followed, in females, and in males as well, by a swelling of the mammae, and, at least in one case, by the production of true milk. Examination of the glands showed that the cells had undergone the changes usual with milk secretion.

Bergell (1898b) suggests in explanation of certain figures for the phosphorus of the blood ash of lactating female animals, in comparison with the normal for the species, that a higher phosphorus content of the blood ash may be associated with the milk producing function, but the data submitted do not warrant a positive assertion to that effect.

DIGESTION OF CASEIN

DIGESTION IN THE STOMACH

Rennet action. Casein, unlike other proteins, is usually introduced into the stomach in the uncoagulated state, and accordingly, a special coagulating enzyme is provided in the rennin. Doubtless the coagulation is a favorable preliminary step in digestion. The conditions of this coagulation, and the steps of the process, have been discussed in the consideration of the chemistry of casein. The casein is first modified to paracasein, and then precipitated with calcium salts. The same action may be brought about by enzymes

occurring in blood, pancreas and other organs. That of the pancreatic juice is probably useful with milk which passes from the stomach uncoagulated. Whether or not the rennin itself has any further action on casein, under favorable circumstances, is uncertain (Van Herwerden, 1907, and others). Paracasein is found to be more easily and more thoroughly digested (*in vitro*) than is the unaltered casein (Hösl, 1910).

Gaucher has reported observations on the time taken for milk and casein to pass on from the stomach, and the physical state in which the casein passes, as shown by duodenal fistulas. Gaucher (1909) observed three stages in this process in a dog. First, the milk passes out as such during the first quarter of an hour; second, during the second quarter of an hour the lactoserum flows out mixed with large clots; and third, the liquid which flows later, colored by bile, contains fine particles of coagulated casein held in suspension. Peptonizing does not take place in the stomach. Gaucher (1911) made similar observations on a child. At a later date Gaucher (1912) showed with a dog that the digestion of casein in the contracted, solid form corresponds only to the third of these stages. According to Gaucher then—of the 7 grams of casein taken in 250 c.c. of milk, 4 grams pass the pylorus in an unaltered form during the first stage; 10-15 minutes' secretion of gastric juice clots the remainder of the milk, and the stomach contractions detach rather coarse fragments of the clot, 1 gram of the casein passing from the stomach in this stage; the other 2 grams contract to a harder mass, which, as the muscular action of the stomach becomes more and more vigorous, is gradually reduced to a purée, this portion leaving the stomach after the lapse of about an hour.

Peptic Digestion. The action of the enzymes of the digestive tract has been studied largely by artificial digestion *in vitro*. Study of this kind with artificial gastric juice was undertaken in 1870 by Lubavin (1870, 1877). It was early known that as a result of peptic digestion there pass into solution albumoses or proteoses (those of casein are designated caseoses) and peptones, and that there remains an insoluble nuclein-like body richer in phosphorus than the casein. This body has been called pseudonuclein or paranuclein, and it has been shown that under favorable circumstances it may be itself digested by the pepsin-hydrochloric acid mixture. On further digestion it is said to become more rich in phosphorus (von Szontagh, 1892, 1893). References to investigations in this field were given in connection with the consideration of comparisons of different caseins in this respect.

According to Chittenden and his associates, (Chittenden and Painter, 1885; Jackson, 1900) the caseoses contain no organic phosphorus, but the paranuclein (which they call dyspepton) always contains over 2 percent of phosphorus in organic combination. A small part of the phosphorus goes into solution as inorganic phosphoric acid.

Clara Willdenow (1893) conducted peptic digestion experiments on casein (*in vitro*), and found split off a phosphorus-containing body, which contains its phosphorus mainly, not as calcium phosphate, but in organic combination, agreeing with Lubavin, but not with Chittenden. This substance, from its properties and phosphorus content, seemed like nuclein or nucleic acid. Willdenow obtained but a single body containing phosphorus and sulphur, not like Lubavin's finding of two such separable by sodium carbonate.

Von Moraczewski (1895a), under Drechsel's direction, studied the distribution of the phosphorus between nuclein and the filtrate from the same after the digestion of casein with pepsin. Various changes of the conditions of the digestion were made, especially as to the concentration of the solution and the duration of digestion. The results given below are taken from the author's table:

PHOSPHORUS OF THE NUCLEIN RESULTING FROM PEPTIC DIGESTION OF CASEIN

Exp. No.	Concentration of casein in solution	Time of digestion	Weight of pepsin	Weight of casein	Weight of nuclein from 100 gm. casein	Nuclein P to 100 gm. casein P	Phosphorus in nuclein
	Percent	Days	Grams	Grams	Grams	Grams	Percent
I	4	8	0.44	14.26	13.60	34.20	2.10
II	4	5	1.38	8.15	14.72	37.50	2.40
III	4	3	1.39	10.19	17.40	44.20	2.19
I	4	2	0.5	3.5	14.84	50.54	0.88
I	6	14	0.5	3.00	3.60	20.66	3.87
II	6	10	0.5	3.00	6.67	29.20	3.13
III	6	7	0.5	3.00	8.31	31.31	2.70
I	0.7	5	1.0	5.27	1.29	6.75	4.10
II	0.7	1	1.0	2.68	4.64	18.20	3.15
III	1.44	7	1.0	5.46	5.96	42.61	6.86
IV	1.44	5	1.0	9.11	8.37	26.17	3.43
I	3.45	2	1.5	33.80	16.48	44.51	2.08
II	3.45	10	1.5	33.80	18.17	52.59	2.27
III	3.51	10	2.0	31.61	17.99	56.40	2.44
IV	3.51	2	1.0	31.61	21.10	63.21	2.82

It was concluded that: "The casein does not have all of its phosphorus in the form of nuclein, for the amount found ranges from 6 to 60 percent, but is never the total phosphorus." "Nuclein from cow's milk does not, even after long digestion, go completely into solution..... The amount is affected by the time of digestion

and still more by dilution. In very dilute solution the amount of nuclein is very small and it is very rich in phosphorus. With longer time of digestion under these circumstances the amount of nuclein decreases and its phosphorus content increases. In concentrated solutions nuclein precipitates in large amount and loses little phosphorus even on protracted digestion." "In the digestion fluid the phosphorus can be precipitated by magnesia mixture directly only after long digestion and in very dilute solution. The degree of dilution plays a greater part than the amount of pepsin or the time of digestion here also....." Von Moraczewski's theory is that the nuclein or nucleic acid from it carries down with it some protein body such as unaltered casein or caseoses.

Sebelien (1895) found 44 and 33 percent of the phosphorus of casein in the paranuclein portion.

Salkowski reported experiments (Salkowski, 1893a, 1893b; Salkowski and Hahn, 1894-95) from which he felt sure that in peptic digestion the main part of the phosphorus of casein remains in solution in some kind of organic combination, only a smaller part being in the insoluble paranuclein. It was further found that the amount of phosphorus in the paranuclein varied with the conditions of digestion, the more unfavorable the conditions, the greater the quantity of paranuclein and the greater also the quantity of phosphorus in the insoluble product. The following table is taken from the article by Salkowski and Hahn.

RESULTS OF PEPSIN DIGESTION OF CASEIN—Percent

Exp.	Paranuclein portion	Albumose portion	Phosphorus content of		Percent of total phosphorus in		
			Paranuclein	Albumose	Paranuclein	Albumose	
II	6.8	93.2	2.41	0.74	19.0	81.0	Conditions most favorable.
III	6.76	93.24	0.55 (?)	0.87 (?)	4.3 (?)	95.7 (?)	
IV	18.5	81.5	2.27	0.59	41.2	58.5	Too little of pepsin solution, or pepsin less active.
V	15.2	84.8	2.18	0.58	41.9	58.1	
VI	21.05	78.95	2.11	0.51	52.5	47.5	

Salkowski (1896a) reported the conditions most favorable to complete digestion, and later (1899) stated that by carrying on the digestion under retarding circumstances he was able to identify an intermediary phosphorus-containing albumose. He says: "The pepsin digestion of casein, then, proceeds in three stages: 1. The transformation of the casein into an albumose, 2. splitting off of paranuclein from this, 3. complete solution of the paranuclein and further digestion of the albumose. While it is not possible sharply to separate the second and third stages from one another,—as during the splitting off of the paranuclein.....a part at least

of it goes into solution,—the distinction between the first and second stages is easy, as the splitting off of the paranuclein takes a definite time, and moreover the process can be interrupted before all the casein has changed to albumose."

Zaitchek (1904) and von Szontagh (1905), under Tangl's direction, made comparative digestion experiments on casein from different kinds of milk, the results of which are evident in the conclusions which we quote from Zaitchek.

"1. By pepsin-hydrochloric acid digestion experiments we determined that woman's, ass's and mare's milk is completely digested, while the casein of cow's, goat's and buffalo's milk under the same conditions of experiment (temperature 38°C., time 72 hours) is only 8, 14 and 15 percent soluble.

"2. Each kind of milk which is not soluble in pepsin-hydrochloric acid without residue leaves a different amount of pseudonuclein from the casein obtained from it. The latter gave without exception 2-3 percent smaller pseudonuclein residue than the milk containing the same amount of casein. The casein precipitated from woman's, ass's and mare's milk is as completely soluble as the milk itself.

"3. The woman's, ass's and mare's milk not only contains an absolutely smaller amount of casein than cow's, goat's and buffalo's milk, but a smaller portion of the total nitrogen, also, is in the casein.

"4. Under like conditions of experiment the different kinds of pure casein give different amounts of pseudonuclein (0-15 percent).

"5. The addition of thymol, toluol and chloroform hinders the casein-dissolving action. The checking effect increases with the amount added.

"6. Both the concentration relations and the duration of action of the pepsin-hydrochloric acid have considerable influence on the solubility of casein in pepsin-hydrochloric acid.

"7. The drying of casein at 110°C. considerably reduces the solubility in pepsin-hydrochloric acid."

Some of Robertson's studies (1906-07, 1907, 1909a, 1910b, 1911, Robertson and Biddle, 1911) on the reversible action of enzymes having been made with casein, this work and his theory regarding the matter may be considered in this connection.

One of the stages in peptic digestion of casein is quite marked because of the difficultly soluble nuclein (or, better, "pseudo-" or "paranuclein") produced. It has been thought that digestion of the

casein from cow's milk could not be carried beyond this point by pepsin, but it has since been shown that under favorable conditions the paranuclein may be made entirely soluble. Now, Robertson has succeeded, by the use of pepsin, in bringing about a synthesis of paranuclein (or one of the constituents of the mixture usually obtained as paranuclein) from the products of complete peptic digestion of casein. The obvious explanation is that pepsin acts as a catalytic agent, accelerating the opposite phases of a reversible reaction, the breaking down of casein into the simpler products, and the union of the simpler products toward the formation of casein. Robertson's theory modifies this interpretation a little in that he thinks that there are two forms of the enzyme active in the two processes. Just as the cleavage products differ from the protein by the elements of water, and may be looked upon as successively more and more hydrated, so the enzyme is supposed to have two forms, the hydrated and the anhydrous. The hydrated form is effective in introducing water into the protein (accelerating hydrolysis), and the anhydrous form, in removing water, so that the simpler bodies unite with one another (accelerating synthesis). The theory is that the effect is brought about by the aid of a temporary union of the ferment with the protein. Representing the two forms of the ferment by HFFOH and FF, and the protein and its cleavage products by HXXOH and HXOH, the types of reaction concerned in the processes under discussion may be shown as follows:

$$HXXOH + HFFOH \rightleftarrows HXXFFOH + H_2O \quad (1)$$

$$HXXFFOH + H_2O \rightleftarrows 2HXOH + FF \quad (2)$$

$$FF + H_2O \rightleftarrows HFFOH \quad (3)$$

In case of hydrolysis (1) represents the union of protein with the hydrated ferment; (2), the breaking up of this union, leaving the protein split, and the ferment in its anhydrous form; (3), the ferment again taking up water to itself from the medium. In synthesis the processes are reversed under the influence of the dehydrated enzyme. The ratio of the velocity of the reaction in the two directions is affected by the concentration of the protein or its cleavage products and of the enzyme, by the temperature, and probably also by the alkalinity or acidity; and this ratio determines the final equilibrium.

Bayliss (1913) believes that Robertson's (1907) synthesis of paranuclein from casein digestion products by the action of pepsin is not a synthesis at all, but a colloidal precipitation without connection with the enzyme.

Küttner (1909) reports a study of peptic digestion of casein from the standpoint of the acidity of its cleavage products. Digestions were made with differences in proportion of gastric juice (from dog), in acidity, in dilution, in temperature and in duration of digestion, with phosphorus and nitrogen determinations on the dissolved and undissolved portions, and in one series on the alcohol precipitable portion of the products of digestion. During one series the digestive products were removed at stated intervals, and fresh mixture substituted. In each case the digestion was stopped at the time that a precipitation of the products of digestion appeared. The nature of the data is evident from the table on p. 268. It will be observed that a considerable increase of acidity occurs during digestion. Of this a certain fraction is spoken of as the non-salt-precipitable acidity, meaning the fraction of the final acidity which is due to some compound not precipitated by thirty percent sodium chloride solution.

The author's conclusions are: "There is every reason to believe that casein is cleaved during peptic digestion into a phosphorus-free and a phosphorus-containing portion. While cleavage of the former continues even under the most unfavorable digestive conditions, the latter (the paranuclein) is less easily digestible, though its further digestibility is such that even under the most unfavorable conditions a fraction is always attacked. By the further digestion of paranuclein under favorable conditions there results a peptically indigestible fraction (Kühne's anticomplex), while the phosphorus-containing constituent which is separated from it by peptid cleavage is further cleaved into more and more highly phosphorized acid-like compounds (paranucleic acids). These are in the main responsible for the increase in acidity of the digestive products observed during the digestion of casein."

According to the observations of Miss Goldthwaite (1910), the presence of carbohydrates retards the peptic digestion of casein, and by an amount proportional to the amount of carbohydrate present.

Long (1907a) made protracted digestions (nearly two months) of casein from cow's and from goat's milk observing the "free" and "total" acid in the digestion mixtures as digestion progressed, the electrical conductivity of this solution, the weights of undissolved and dissolved solids, and the conductivity and acidity of this dissolved solid on being redissolved after evaporation. During digestion the electrical conductivity values, and the total and free acidity varied regularly. Both acidity values were lower for the goat casein than for cow's casein. A larger residue of pseudonuclein was finally left from the casein of goat's milk; the dissolved substances were thought to be similar in nature.

PEPTIC DIGESTION OF CASEIN UNDER DIFFERENT CONDITIONS OF ACIDITY

Digestion fluid			Digestion time	Increase of acidity N/20 sol.	Percent non-salt-precipitable acidity	Undigested residue	Dissolved material	Percent dissolved		Ratio of percents dissolved	Phosphorus content of residue
Gastric juice cc.	Added HCl cc.	Total acidity N/20 sol. cc.	Hours	cc.		Percent	Percent	P	N	P:N	Percent
5	...	17	1 5/6	16.6	....	68.65	21.34	15.9	26.16	100:164.5	1.07
10	....	34	1 1/2	29.6	....	52.69	37.31	21.6	42.83	100:198	1.28
10	17.0	51	1	34.5	37.9	34.36	55.64	29.84	55.50	100:186	1.77
15	8.5	60.5	1	44.6	39.69	30.82	59.18	33.52	62.97	100:188	1.87
20	....	68	1	52.9	44.1	27.62	62.38	36.32	68.84	100:189	2.0
25	....	85	1	70.0	43.0	20.58	69.42	43.09	78.56	100:182	2.4
25	25	110	2 1/2	84.4	54.3	17.04	72.95	53.39	84.36	100:157.9	2.37
25	25	140	4 1/3	91.6	53.9	16.12	73.88	55.2	86.96	100:157.5	2.41

Amount of casein, in each case, 5.0 gm. (10 percent moisture); volume of solution 300 c.c.

DIGESTION IN THE INTESTINE

In the intestine the casein, whether still unaltered, or changed by the pepsin to proteoses and peptones, can be further split by the trypsin of the pancreatic juice and the erepsin of the intestinal secretion (Hammarsten, 1911). The paranuclein from casein is also actively digested by trypsin.

Brugsch and Masuda (1911) state that the intestinal juice can not digest casein, though an extract of the colon bacillus does so, and that the feces do not possess a casein-cleaving capacity if the pancreatic secretion be excluded.

The absorption of the cleavage products of casein takes place at least principally as amino acids. The form in which the phosphorus of casein is absorbed has not been determined.

Artificial Digestion Tests. Sir William Roberts (1879, 1881) first noticed the curdling of milk by pancreatic extract; also that the first principal phase of the tryptic digestion of casein is the formation of a modification of the casein, which he and others since have called metacasein. In both of these respects the action is very similar to that of rennet, as others have noted (Edkins, 1891; Halliburton and Brodie, 1896). Harris and Gow (1892) found the action lacking in the pancreas of some animals.

Von Szontagh (1894) states that on digestion with pancreatic juice the casein is first entirely dissolved, and then a precipitate forms. In an alkaline solution the precipitate is less, but evidently because of a solvent action of the alkali, and not because of digestion of the nuclein.

Sebelien (1895) reports digestion experiments with pancreatin-soda solution. Below are the author's figures for his fourth and fifth series of experiments, in which, with two different concentrations of casein solution, increasing amounts of pancreatin solution were used (the total volume of digesting solution being kept at 300 c.c. by regulation of the volume and concentration of the soda solution added). In this case the residue precipitated on acidifying

DEGREE OF DIGESTION OF CASEIN AND ITS PHOSPHORUS BY PANCREATIN

Time of digestion	Casein solution	Pancreatin solution	Soda Percent	Casein undissolved Percent	Phosphorus undissolved Percent
18 hours.....	200 cc., 2.076%	10 cc., 5%	0.167	1.2	2.2
" "	200 cc.	20 cc.	0.167	2.3	2.3
" "	200 cc.	40 cc.	0.167	2.5	2.3
8 hours.....	200 cc., .556 %	25 cc., 1%	0.208	2.5	2.1
" "	200 cc.	50 cc.	0.208	3.5	1.6
" "	200 cc.	75 cc.	0.208	2.5	1.2

the solution after a certain time of digestion was weighed, and tested for phosphorus. This residue was considered to be undissolved casein. It was but a small percent of the casein by weight, and was not like the pseudonuclein, which forms a much larger part of the casein. As the figures show, the casein and the casein phosphorus were practically completely digested.

Rotondi (1902) reports that casein, from either human or bovine milk, is much more readily digested than fibrin, by both pepsin-hydrochloric acid and pancreatin, the digestion by pancreatin being especially easy.

E. Fischer and Abderhalden (1903) say that more hydrolysis of casein takes place by the combined working of pepsin-hydrochloric acid and pancreatin than by pancreatin alone.

Biffi (1898), using a pancreatic ferment prepared from beef pancreas, concluded that under favorable conditions casein is completely digested by that enzyme, about 4 percent splitting off as tyrosin, with the formation of primary and secondary albumoses and an antipeptone which correspond to those of fibrin. All of these products are probably free from phosphorus; but in the soluble product phosphorus is always present in two forms, a part being directly precipitable by magnesia mixture and another part being so precipitable only after fusion with soda and potassium nitrate. The phosphoric acid increases with the duration of digestion and with the amount of ferment, at the expense of the organic phosphorus. The organic can further be changed into inorganic by the action of dilute alkali solution or by boiling with barium carbonate.

From the tube digestions made by Rachford (1900) it may be said that pancreatic digestion of the casein of cow's milk is facilitated by the presence of maltose solution, of lime water, or of 0.4 percent sodium carbonate solution. Hydrochloric acid was found very slightly to retard the action of pancreatic juice alone, but greatly to increase the action in the presence of bile. "Bile assists the pancreatic juice in the digestion of casein, but it renders even greater assistance when the casein is partly saturated with hydrochloric acid."

Plimmer and Bayliss (1906) studied the action of enzymes and of alkali on casein. They summarize their results as below:

"1. The whole of the phosphorus of caseinogen, except for a very small residue, is converted into a soluble form by the action of trypsin in 24 hours.

"2. The curve of its rate of separation is exactly parallel to the curve of the electrical conductivity (see Bayliss, 1904) during the first 7-8 hours; its rate of separation after this time is less rapid.

"3. The small insoluble residue is partly derived from the trypsin, and partly from the caseinogen, and consists most probably of the products of decomposition of nucleoproteid.

"4. The 'soluble P_2O_5' consists of inorganic phosphoric acid—35 percent— and organic phosphorus, 65 percent.

"5. The phosphorus of caseinogen is very slowly converted into a soluble form by the action of pepsin. The quantity thus changed is only 70 percent in 149 days, and consists, except for a negligible quantity of inorganic phosphoric acid, of organic phosphorus.

"6. Papain, in its action on caseinogen, is intermediate in power between pepsin and trypsin. In its rate of splitting off of 'soluble P_2O_5' and 'soluble nitrogen' it resembles trypsin the more closely, but it is much slower.

"It acts best in a neutral or faintly acid medium; its action is slower in a slightly alkaline medium and is almost inhibited by 0.5 percent sulphuric acid and 0.5 percent sodium carbonate.

"7. Ovovitellin, containing lecithin, is very slowly digested by trypsin in comparison with caseinogen. Only one-half of its phosphorus is converted into a soluble form in 36 days. A similar quantity is probably contained in the lecithin portion of the molecule.

"8. One percent caustic soda converts the whole of the phosphorus of caseinogen into 'soluble P_2O_5' in 24 hours. It resembles trypsin very closely in its rate of action.

"9. The 'soluble P_2O_5' produced by one percent caustic soda in 24 hours consists entirely of inorganic phosphoric acid. In the same time the quantity of 'soluble nitrogen' scarcely increases.

"10. The organic phosphorus produced by the action of trypsin on caseinogen is not completely converted into inorganic phosphoric acid by the action of one percent caustic soda. The total quantity of inorganic phosphoric acid produced by trypsin and subsequently by one percent caustic soda is 50 percent of the total phosphorus of caseinogen."

Robertson (1906-7), from his study of tryptic digestion of casein in relation to the ion-proteid theory, concludes (in part) that neutral caseinates in solution undergo fairly rapid autohydrolysis; that the velocity of hydrolysis of calcium caseinate by trypsin at moderate substrate concentration is directly proportional to the amount of trypsin present—at higher substrate concentrations the rate of increase being a little greater. A variety of salts (including disodium phosphate) were found to accelerate in different degrees the

velocity of the hydrolysis of calcium and sodium caseinates; monosodium phosphate had a retarding influence. The special study of the part played by the alkali in the hydrolysis of proteins by trypsin (Robertson and Schmidt, 1908), the alkalinity being followed by means of the gas-chain, brings out facts against the view that the OH^- ions in a tryptic digest play the part of an accessory catalyzer, though it is suggested that the real catalyzer in these systems may be a hydrolyzable compound of trypsin with the base present. The investigations of Walters (1912a, 1912b) are a continuation of that of Robertson.

ANIMAL EXPERIMENTS WITH CASEIN

Sandmeyer (1895), testing the possibility of the absorption of the paranuclein from casein, introduced such paranuclein into a dog by means of a probe, and judged of its absorption by phosphorus determinations in the urine. If one may draw any inference from such an observation, something more than ⅓ of the paranuclein was absorbed. The dog received only water for two or three days before the introduction of the phosphorus compound, and the urine showed 0.33-0.37 grams P_2O_5 per day; on the paranuclein days 2.864 and 4.296 grams, respectively, of P_2O_5 were introduced, and caused 1.34 and 1.84 grams to appear in the urine; in each case on the day following the experiment the urinary phosphorus returned to its previous value (0.33 and 0.30 grams P_2O_5).

Salkowski (1901) fed the iron compound of his so-called paranucleic acid to rabbits. Absorption occurred, as judged on the evidence of finding the iron content of the livers of the rabbits which received this iron compound appreciably above that of those which had a corresponding diet without this substance, and above that of those which received iron in the form of its combination with atmidalbumose (an albumose derived from fibrin), or as ferratin.

Another study on the absorption of products of the decomposition of casein is that of E. Voit and Zisterer (1909-10) on dogs. They compared the nitrogen-sparing value of undigested casein with that of the products of pancreatin digestion, and those of acid hydrolysis of casein. The conclusion is that the physiological value of protein bodies is unfavorably influenced by a deep cleavage, and that, in general, protein bodies do not undergo complete cleavage in the digestive tract, but that certain complexes are absorbed unchanged. No observations were made with regard to the phosphorus of the casein or its decomposition products.

These conclusions are almost identical with those of Abderhalden and Rona (1904, 1905) from their observations as to maintaining life in mice and meeting the nitrogen requirement of a dog.

With regard to the mice, the report is that the products of pancreatin digestion of casein serve about as well as pure casein, while those from the combined digestion by pepsin and pancreatin (further split) are of less value. Mice fed with the latter, however, live longer than starving mice, while those fed with the products of acid hydrolysis do not. The results with the dog were of like import. In later work, however, Abderhalden (1912) showed that dogs are able to maintain nitrogen equilibrium and retention on products of either acid or enzymatic splitting of proteins, or on a mixture of recognized amino-acids.

Marcuse (1896, 1897) carried out nitrogen and phosphorus balance experiments with dogs on a mixed diet in which, in some cases, the protein given was in the form of casein, and in some cases in the form of flesh. In either case a salt mixture including phosphates was given with the other food, and the conditions were generally too complex for definite inferences; but, on the whole, both nitrogen and phosphorus retention were greater for the casein periods than for the flesh periods.

Schreiber and Waldvogel (1897) report 15 cases of various diseases in which "Sanose," a protein preparation containing 80 percent casein and 20 percent albumose, was taken with the food or used in its preparation. It was found useful in cases where meat was either a distasteful or an undesirable article of diet. Urine analyses are submitted.

Knoepfelmacher (1898a, 1898b, 1899, 1900) studied the use of the casein of milk by infants and older children by a comparison of the nitrogen and organic phosphorus of their feces with the casein nitrogen and phosphorus ingested. The methods used in the earliest work, comparing the use of mother's milk and cow's milk, he says later were faulty. The following table from Knoepfelmacher's latest work shows no important percentage differences in the digestion of either the nitrogen or phosphorus of casein by infants and older convalescent children.

NITROGEN AND PHOSPHORUS OUTGO IN THE FECES FROM A DIET OF COW'S MILK—INFANTS AND OLDER CHILDREN

Age of child	Length of experiment	Intake				Outgo in feces		
		Milk	Casein	Casein N	Casein P	N	Total P	Organic P
	Days	cc.	Grams	Grams	Grams	Grams	Grams	Grams
11 yrs.	4	13,250	296.19	46.498	2.517	3.6088	8.33	0.1225
8 yrs.	3	10,681	341.01	53.538	2.898	3.54	6.68	0.12
7 yrs.	3	8,815	277.64	43.5913	2.3599	1.723	3.645	0.1229
4¾ mos.	5	4,770	112.21	17.6169	0.9537	1.238	1.149	0.0526
5 mos.	4	3,498	79.56	12.49	0.6762	0.928	0.914	0.0237
6 mos.	5	4,400	60.52	9.683	0.514	0.664	0.478	0.0264
8 mos.	5		73.91	11.825	0.628	0.6513	0.856	0.0343

Prausnitz and his associates (Micko, Müller, Poda and Prausnitz, 1900; Poda and Prausnitz, 1900; Micko, 1900; Müller, Paul, 1900) made similar feces studies with older people. In the introductory article the whole work is summarized, with a discussion of the general conclusion that the feces are made up in the main of residues from the digestive juices, rather than of food residues, the amount of such juices being modified by the kind of food taken. Poda and Prausnitz concluded that casein, in the form of the preparation called "Plasmon," was utilized as well by healthy men as the flesh with which it was compared. Micko looked for paranuclein and for nuclein in the feces. Both were found in the feces from both these kinds of diet, and from ordinary mixed diet; of each the plasmon feces showed less than the flesh feces. Paul Müller concluded that a diet of cow's milk leaves, with neither infants nor adults, a phosphorus-rich casein residue in the feces.

Cronheim and Erich Müller (1900, 1902) compared the usefulness, to children, of lecithin and casein, by feeding milk-powder with and without added egg-yolk. The periods were very short; the results were variable, and the observations are not very significant. In these, and in similar feeding experiments on dogs and on guinea pigs, there was thought to be somewhat better storage of nitrogen from lecithin-containing food than from casein.

Comparisons of Raw and Sterilized Milk. Jemma (1899) reports from his comparison of the action of enzymes on sterilized and unsterilized milk that pepsin-hydrochloric acid digests unsterilized milk more quickly than sterilized, while both pancreatin and rennin digest the sterilized more quickly. The addition of rennin, pepsin and hydrochloric acid together caused during the first four hours a greater digestion of sterilized milk, but by longer-continued digestion the unsterilized milk showed a greater peptone mass. By the successive action of pepsin-hydrochloric acid for 15 minutes, then rennin, then pancreatin and bile for 4 hours, the sterilized milk was more completely digested.

Cronheim and Erich Müller (1903, 1908) made raw and sterilized milk tests with children,—both healthy children and children having rachitis. With the healthy children no differences in favor of either milk could be established, nor were there marked differences in the rachitic children.

Other feeding and metabolism experiments involving the use of casein are those of Gumpert (1905), L. Jacob (1906), Lipschütz (1910a, 1911b) and Osborne and Mendel (1911a, 1911b and others).

Summary. No satisfactory theory as to the production of casein in the milk glands can be offered from the evidence at hand, nor even as to whether the phosphorus for the same is obtained directly from gland nucleoprotein or from the blood.

Artificial digestion tests made with juices or enzymes from the stomach show that casein is but slowly acted on by such enzymes, and that the early stages of the process tend to leave the main part of the phosphorus in the form of a difficultly soluble paranuclein, which may, however, in time, be nearly or quite entirely dissolved; and that the phosphorus-free products formed are always more readily further cleaved than are those containing phosphorus, so that the undissolved residue becomes constantly richer in phosphorus. It is shown also that the phosphorus which goes into solution during these processes is partly inorganic and partly organic in form; and that the results, and the ease and rapidity of the action of pepsin on the paranuclein are variable for the casein obtained from different species of mammalia, the completeness and speed of digestion being greater for the casein of woman's, ass's and mare's milk than for that of cow's, goat's and buffalo's milk. The presence of carbohydrate retards peptic digestion. The ferment-protein reaction which brings about cleavage, may, under favoring conditions, be reversed.

With regard to the enzymes of the intestine, tests *in vitro* indicate that activated trypsin may cause a completion of the digestion of casein as to both its nitrogen and its phosphorus portions; that the phosphorus thus passing into solution (very nearly all of that of casein) is more largely organic than inorganic; that the portion of the phosphorus converted into inorganic phosphoric acid increases with the duration of digestion and with the amount of ferment present; that cleavage proceeds further and more easily under the influence of both pepsin and trypsin than of either alone; and that bile assists trypsin digestion.

Experiments on living subjects seem to show an efficient absorption and use of the constituents of casein by both animals and human beings, older and younger, perhaps even better than the use made of flesh. Undigested casein, however, has been found to serve the body better than do the products of complete pancreatin or acid cleavage (dogs and mice), indicating that within the organism there is some absorption of casein in a state of incomplete digestive cleavage. Dogs have, however, been maintained in nitrogen equilibrium on the products of complete cleavage.

Evidence has been produced that of ingested milk large portions (four-sevenths of the whole) pass the pylorus unaltered, and later the rest of the casein passes in larger or smaller clots, not peptonized.

While pepsin-hydrochloric acid digests unsterilized milk more quickly than sterilized, yet under the influence of the succession of enzymes present in the digestive tract, the sterilized is said to be more completely digested. So far as we learn, experiments with children have not demonstrated any practical advantage as due to either condition.

THE METABOLISM OF THE COMPOUNDS OF GLYCERO-PHOSPHORIC ACID

THE FUNCTION OF LECITHIN IN INTERMEDIARY METABOLISM

The method of usefulness of lecithin in its more intimate relations with the life of the animal has been a subject of much speculation, but little productive study. A considerable number of theories have been advanced, which we mention in brief.

Bergell (1898b) concluded that in animal as in vegetable cells organically combined phosphorus stands in a causal relation to the function of cell cleavage. Lecithin and nuclein phosphorus, as universal cell constituents, may at least be regarded as necessary to cell cleavage.

Loew (1899) suggested that the chief function of lecithin is to serve for respiration, it being the form into which fat must be changed to become combustible in the protoplasm. According to this theory, by the transformation of fatty matter into lecithin the higher fatty acids are offered to the protoplasm in a soluble form, and, after being oxidized, other molecules of fatty acids may enter into the place of the former; thus the same molecules of glycerophosphoric acid serving repeatedly as vehicles for oxidation of molecules of fatty acids.

The idea of the service of lecithin as a storage product has often been suggested. Hanai (1897) considers it in this light. He observed that old tea leaves lose their lecithin in the spring, while the amount of it increases gradually in the young leaves. In the bark of *Prunus cerasus* the lecithin also decreases as the flower buds form and open.

The metabolism of lecithin during the incubation of eggs, as shown by the work of Maxwell (1893), Mesernitzy (1907), Carpiaux (1908), and Plimmer and Scott (1909) (see Incubation) also suggests a storage function; an accumulation in anticipation of rapid cell multiplication.

Springer (1902) says that lecithins are present most abundantly where growth is most active, and that they diminish when the seat of growth shifts to some other place.

One instance in harmony with this theory is the comparative richness of the marrow of young bones in lecithin. Its abundance in gland cells, eggs, spermatozoa and pollen (Stoklasa, 1896b) also suggests a connection with intense metabolism, but surely no such idea is exemplified by the high lecithin content of nerve tissue.

Burow (1900) finds that the lecithin of the milk of cattle, dogs, and human beings varies directly as the total protein of the milk, and also as the weight of the brain of sucklings of the different species, in relation to their body weight; that is, the greater the relative brain weight, as compared with body weight, the higher is the lecithin content of the milk, reckoned in percent of the protein. The figures are as follows:

Species	Lecithin of milk Percent	Protein of milk Percent	Lecithin: Protein X:100	Brain:Body weight
Cow	0.054	3.87	1.40	1:370
Dog	0.170	8.05	2.11	1:30
Human	0.580	1.90	3.05	1:7

Glikin (1908a) compared the lecithin content of the bodies of several species of young birds and mammals, and found that it varied directly as the helplessness at birth. He suggests an essential connection.

Parrozzani (1909) believes that lecithin represents the final stage by which non-nitrogenous organic substances acquire the power of combining with nitrogen, especially with amino acids, for the synthesis of albuminoid substances.

Hammarsten (1905b) suggests a possible connection between the lecithin content of the bile and the amount of fat to be digested, and cites the very high lecithin content of the bile of the polar bear.

Daniel-Brunet and Rolland (1911a) suggest the origin of a part of the biliary lecithin by the observation, which we have not seen substantiated, that the lecithin of the bile of the bull is decreased by castration.

As results of his studies of the phosphatids W. Koch has made a number of suggestions as to the function of lecithin. In brief they are as follows: In an early article (1902a) he advanced the idea that the emulsion formed by the lecithins may be the substratum in which the reactions of the cell take place. The precipitation of this emulsion by divalent cations is prevented by univalent and trivalent cations, as far as investigated, and this observation may furnish an explanation of the changes brought about by electrolytes in the living cell.

Somewhat later (1903) Koch suggests that the lecithins of the cell may have two values: (1) They, together with proteins in colloidal solution, may furnish the basis for bringing about the necessary viscosity, by the facility with which they are influenced by sodium and calcium ions. (2) They share in the metabolism of the cell, and especially by their unsaturated fatty acids and methyl groups bound to nitrogen, in causing reactions as yet not understood.

Koch (1905b) noted the constancy of the creatinin excretion by men and a dog, and suggested that the lecithins of the food furnish the methyl groups of the creatinin excreted.

Two years later Koch (1907a) also made a physico-chemical study (colloid precipitation and measurement of viscosity) of lecithin and cephalin which may have a bearing on their significance in the red blood cells.

Writing on the significance of phosphatids for the living cell, Koch (1909b) says, —"Reactions may be carried out with colloidal solutions of phosphatids which are very much like those observed with physiological material, both qualitatively and quantitatively. Both carbonic acid and ammonia influence lecithin emulsion even in small concentration, as was to be expected from the H^+ and OH^- concentration, respectively. Therefore the phosphatides play an important part both in the morphological and the chemical differentiation of cells, in that they are able to form precipitation membranes, which one may think of as distributed throughout the protoplasm."

Koch *et al* (1910)* made a series of pharmacological studies on the phosphatids, especially with reference to their participation in the selection and transmission of substances through the membranes of the cell. Among their conclusions are the following:

"The greater concentration of potassium in the cells of a tissue as compared to the surrounding lymph spaces or serum can be in part accounted for by the specific affinity for this element of some of the phosphatides, especially kephalin."

"There is no evidence that anaesthetics or hypnotics produce changes in the state of aggregation of lecithin or kephalin, which are sufficiently consistent to account for such a general phenomenon as narcosis. There is some evidence, however, that chloroform, as distinguished from pure ether, has the power to form a combination with lecithin, a phenomenon which may be brought into relation with its slow elimination and consequent tendency to produce delayed poisoning."

* W. Koch, 1910b; Koch and Pike, 1910; Koch and McLean, 1910; Koch and Williams, 1910; Koch and Mostrom, 1910.

Considering the possible participation of the phosphatids, through specific chemical affinities, in the translocation of metabolites, these authors reached conclusions a part of which are as follows:

"The changes in state of aggregation of lecithin produced by sodium chloride are the result of the independent action of the sodium and chlorine ions, whose effects are in opposite directions. Below the concentration of a physiological salt solution (0.12 molecular) the action of the chlorine ion, which decreases the state of aggregation of the lecithin, predominates. Above the concentration of a physiological salt solution, the action of the sodium ion, which tends to increase the state of aggregation of lecithin, comes more and more into prominence.

"It has been suggested that, when the phenomenon of chloride retention occurs, some change has taken place in the state of aggregation of the cell lipoids which allows this action of the chlorine ion to predominate to a still greater extent.

"Ammonia and bile salts possess the power of altering the physical state of aggregation of lecithin to such an extent as to permit of the conclusion that they can be of functional significance in altering the permeability of cell membranes.

"The ability of the tissue metabolites to combine with lecithin, as measured by the changes in the physical state of aggregation produced by their presence, is in some cases considerable, in other cases entirely lacking. Thus hypoxanthin, creatin, creatinin, adrenalin and ammonia salts show evidence of combination. Inosite is doubtful, and urea is negative.

"The amino acids show varying powers of combination. The dicarboxy-acids, like acids in general, tend to increase the state of aggregation of lecithin.

Studying the function of the brain phosphatids in the action of strychnin they conclude:

"The central nervous system, especially the cord, by its high phosphatide content, is enabled to pick the strychnin out of the blood stream on account of the affinity of the lecithin and kephalin for the strychnin as compared to serum albumin. The strychnin probably enters into the combination with lecithin through some relation to its unsaturated fatty acid group (oleic acid).

"Strychnin interferes in such a way with the normal relation of these unsaturated fatty acid groups to oxygen as to bring about a more rapid transfer to any easily oxidizable substance."

Loewe (1912a, 1912b, 1912c, 1912d) made a series of physicochemical studies of lipoids in relation to organic solvents and coloring matters, the object being to determine the nature of lipoid action, biologically and pharmacologically.

The following quotation expresses his conclusion:

"The hypothesis of the solvent function of lipoids and the associated theory of the taking up of substances by the cells and of narcosis is not supported by the examples studied. The study of the 'taking up' by lipoids of the substances considered in this theory shows that the process does not follow the Henry-Nernst absorption laws, but is an adsorption.

"The taking up by lipoids of basic coloring matters, organic solvents and organic substances dissolved in water is not a linear function of the concentration, but is determined by an adsorption isotherm. Therefore it is not to be expected that the lipoid components of the cell membrane, so far as they are not very freely movable on the cell contents, will serve to facilitate the taking up into the interior, but rather their action will be hysteresis."

Reicher (1911) believes that the physiologic oxidation of fat, in general, is made possible only through combination in lecithin, an idea in harmony with that of Loew (1899). The feeding of lecithin-free fats, and the perfusion of a surviving liver with blood and triolein increased the lecithin of the blood.

Kovaliova (1912) compared lecithin and other phosphorus compounds with reference to their effects on the power of oxidation in rabbits. The phosphorus compounds were administered by subcutaneous injection in oil suspension. Two hours later the rabbits were injected with 2 gm. benzene, and placed in an apparatus where the respiration coëfficient and power of oxidation were determined. Five-hour and 24-hour experiments were performed.

Lecithin caused an increase in the elimination of phenol, and increase in the respiration coëfficient. Sodium nucleate in small doses caused an elevation, but in large doses a depression, of respiration coëfficient and degree of oxidation. Sodium glycerophosphate caused a depression of the respiration coëfficient, but a greater increase of the degree of oxidation than that of the two preceding substances. Phytin in aqueous suspension caused an increase in the degree of oxidation, but scarcely affected the respiration coëfficient. In Kovăliova's judgment lecithin exerted the more uniform influence on the elevation of the respiration coëfficient and degree of oxidation, while the sodium nucleate, in large doses, exerted the most uniform action in lowering them.

Stuber (1913a, b) determined the effect of lecithin and cholesterol on the phagocytic index of leucocytes. Cholesterol diminishes the index. Lecithin does not affect it, but prevents the action of cholesterol. The oleic and palmitic acid esters of cholesterol also check phagocytosis, but lecithin does not prevent this action.

Maslow (1913) studied the effects of lecithin and other phosphorus compounds on the functions of the intracellular ferments of dogs. Several litters of young dogs were the subjects of these experiments. One was used as a control, being killed at the beginning of the experiment; and a second control was fed the usual mixed meat diet, and was then killed before the close of the experiment. The remaining animals were divided into four groups. One received a low-phosphorus broth containing protein, carbohydrate and fat in sufficient quantity; another group received the same broth plus a phosphate; a third, the same plus glycerophosphate; and a fourth, lecithin. The second group received either whole milk, or a milk preparation in which the casein was replaced by albumin.

Under normal conditions of development there was in all organs a normal development of fermentative energy. On the phosphorus-poor ration the animal declined in weight, and died. The phosphorus content of the organs decreased, the decrease being mostly in the inorganic phosphorus. Of the organic phosphorus only the lipoid phosphorus decreased. The ferment function of the organs was markedly disturbed; the catalase, lipase, amylase, diastase, and nuclease were depressed in amount or checked in their development.

The addition of inorganic and glycerophosphate phosphorus to the diet were without avail. The organs showed phosphorus impoverishment and the intracellular enzymes were not favorably influenced. Lecithin, however, increased the phosphorus content of the organs, especially their organic phosphorus content, and stimulated the development of the ferments.

The author concludes that abundance of assimilable phosphorus in the food runs parallel with abundant ferment formation in the organism, and that a power of the animal to synthesize organic phosphorus compounds is not probable. For therapy the conclusion was drawn that the use of phosphates and glycerophosphates should be limited, and that lecithin is to be preferred, if increase of the phosphorus content of the organism or activating of the ferments is desired.

Mayer and Schaeffer (1913) find that the lipoid content of tissues tends strongly to remain characteristic of the species and tissue, neither fasting nor overfeeding producing characteristic change, this proportion therefore, appearing to be fundamental and

permanent. The ratio of fatty acids to lipoid phosphorus is remarkably constant in certain types of cells in different animals, as for instance in kidney and red blood cells. A relation is shown to exist between the capacity of tissues to imbibe water, and the ratio of lipoid phosphorus to cholesterin. In all the species examined the various organs compared as to lipoid phosphorus content (on the fresh basis) in the same order; their content of lipoids apparently being related to physiologic activity, in ways yet to be explained.

Lecithin and other phosphatids of the blood corpuscles and of the tissue cells also stand in important relations to the action of poisons of various sorts and origin, an important subject which has not been included in this investigation.

THE INFLUENCE OF LECITHIN IN DIGESTION

There is prevalent an idea that lecithin is of functional value in the alimentary digestion processes, but the experimental evidence on the subject is not all in support of the theory. Thus Kalaboukoff and Terroine (1907a, 1907b, 1907c) tested lecithin in relation to the cleavage of monobutyrin and olive oil; also as to its influence in activating pancreatic juice to such cleavage, with and without the presence of bile salts. Such activation by bile salts was quite evident, whether with or without lecithin; but lecithin showed no such activating power in the case of monobutyrin, and only a slight influence, and at relatively high concentration in the case of olive oil. This conclusion is in harmony with those of O. vonFürth and Jul. Schulz.

In the second paper were reported similar tests of the activating power of lecithin, and of bile salts with gastric and intestinal juices. "1. The lipase of the glycerin extract of gastric mucous is not at all changed by the addition of lecithin; it is notably retarded by bile salts. 2. The intestinal lipase is not at all modified by the addition of lecithin; it is activated by bile salts."

The third paper had to do with the action of ovo-lecithin on amylase, trypsin and rennet. "Addition of lecithin does not modify saccharification of starch, the digestion of casein and coagulated albumin, nor the coagulation of milk by pancreatic juice; the addition of bile salts activates plainly the coagulation of milk by kinased pancreatic juice."

In a later paper (Kalaboukoff and Terroine, 1909) cleavage of an emulsion of pure lecithin (prepared from egg yolk) by pancreatic juice at 40° was tested by the acidity developed. No increase of acidity was detected when boiled pancreatic juice was used, and but slight increase when unboiled juice was used; this was a little further increased by the presence of bile salts; but even after 66 hours the acidity was but slight (not more than equivalent to

2.8 c.c. of N/20 NaOH for 10 c.c. of the mixture). These authors think that the results found by Stassano and Billon (1903a, 1903b) should be referred to cleavage of fatty substances obtained in the course of preparation.

Regarding some other phases of this matter these authors say: "The work of Slowtzoff and of Stassano and Billon has shown that lecithin is absorbed and appears in lymph. Bayer has found, and so do we, that if a solution of bile salts be added to a milky lecithin emulsion a clear liquid results. Ultramicroscopically, lecithin emulsions have a colloidal appearance, with an infinite number of grains, and these almost disappear after the addition of a solution of bile salts."

As a result of recent investigations, Terroine (1911) repeats his conclusions: (1) Lecithin does not increase the rate of hydrolysis of monobutyrin by pancreatic juice, and increases only slightly in more concentrated solution the rate of hydrolysis of oils. (2) It increases the lipolytic action of neither mucous membrane of stomach (in glycerol) nor intestinal lipase. (3) It has no action on the rate of hydrolysis of starch, the digestion of milk casein or coagulated albumin, or the coagulation of milk by pancreatic juice.

On the other side of this question we have the work of Moore and Parker, Hewlett, Loevenhart and Souder, Küttner and Usuki as mentioned in brief below.

Moore and Parker (1901) state that the presence of lecithin greatly increases the solvent power of bile toward fatty acids and soaps. The bile salts serve to keep lecithin and cholesterin in solution, and hence aid in their emulsification by the liver. The combination of bile salts and lecithin accomplishes the solution of the fatty acids and soaps. Numerical results from this study are given below.

SOLUBILITY OF FATS AND SOAPS AS AFFECTED BY BILE SALTS AND LECITHIN

	Distilled water	Bile salts, 5 percent	Bile salts, 5 percent +lecithin, 1 percent
Free fatty acids			
mixed	Practically insoluble	0.5% soluble	0.7% soluble
oleic	Less than 0.1% soluble	0.5	4.
palmitic	" " "	0.1	0.6
stearic		Less than 0.1%	0.2
Sodium salts			
mixed	2.23% apparently colloid sol.	Not tried	Not tried
oleate	5.0% soluble	7.6%	11.6%
palmitate	0.2	1.0	2.4
stearate	0.1	0.2	0.7
Calcium salts, oleate	(Less than 0.1%)	0.2	1.4
palmitate	(Much less than 0.1%)	Less than 0.1%	0.9
stearate			0.4
Magnesium salts, oleate	(Less than 0.1%)	3.2	8.2
palmitate	(Much less than 0.1%)	0.2	1.2
stearate		Less than 0.1%	1.0
Lecithin	Practically insoluble	7.0%	...
Cholesterin	Absolutely insoluble	About 0.1%	Not more than 0.15%

Reiss (1904) determined that lecithin, with chloroform, is able to take up the ferments rennet and trypsin, as neither constituent alone can, and as no other fat tried can with chloroform. It is thought that this may have some significance with reference to the rôle of lecithin in the body. This is likened to the activating power of lecithin toward the haemolysis of cobra poison.

Hewlett (1905) studied the action of lecithin in bile on fat digestion by pancreatic juice of a dog. Bile increased the action of pure pancreatic juice on triacetin. (Fat was not used, to eliminate the factor of influence through emulsification. Triacetin is a soluble glyceride.) Bile served to increase the action of pure pancreatic juice on this ester, especially in the first hour. Boiling the bile does not destroy this property, and furthermore, it was found not to reside in cholesterin or the pigments, and was found not to depend on variations in reaction, nor on variation in the amount of calcium salts present. Precisely the same effects of acceleration were produced, however, by the addition of lecithin to the pancreatic juice. Hewlett suggests that this influence is of the nature of a "zymoexcitor."

Loevenhart and Souder (1906-7) investigated the relations of lecithin to the digestion of the higher fats by quantitative determinations of the activity of pancreatic juice on olive oil, ethyl butyrate, diacetin, triacetin, ethyl acetate and ethyl propionate in the presence and absence of bile salts, and bile.

Bile salts, lecithin and bile greatly accelerate the action of pancreatic juice on all the esters studied. The effect of these accelerators differs with the particular ester, and differences of experimental conditions greatly alter the degree of acceleration, and the relative activity of the bile salts and lecithin. These accelerating capacities are considered to depend to a certain extent on their solvent action, and also on their action on the enzyme in some other way.

Küttner (1907) determined, *in vitro,* the effect of lecithin on the peptic digestion of casein, and on pancreatic digestion of monobutyl glycerin. Lecithin in certain proportions accelerates the enzyme action of gastric or pancreatic juice; in other greater proportions it retards it. Curves were plotted exhibiting this action. The cause of this action was not determined.

Long and Gephart (1908b) report that bile salts, as ordinarily obtained, carry down a phosphorus complex, which, by Hammarsten and others, is regarded as lecithin, and also that bile salts are capable of dissolving and holding 80 percent of their weight of egg lecithin.

Usuki (1910) studied the influence of lecithin on fat digestion in the stomach, and in the intestine, by the feeding of dogs; and after certain lengths of time the dogs were killed, the different portions of the alimentary tract separated by tying, and the contents removed and analyzed. The results seem unmistakable. The author's conclusions are as below.

1. According to these experiments the digestion of fat took place more slowly after feeding of milk than after feeding of milk-lecithin or milk-yolk mixtures which left the stomach 1½ to 2 hours sooner than the milk alone. While of the pure milk, after six hours, only half had left the stomach, the same result was obtained with the mixtures in four hours.

2. After taking milk more soaps are found in the contents of the small intestine than after the taking of milk-lecithin mixture. On the other hand, after taking milk-yolk mixture, more soaps were found in the feces. This contradictory relation between the contents of the small intestine and the feces is probably to be explained by absorption in the large intestine.

3. Splitting of lecithin in the stomach takes place more quickly than splitting of neutral fat.

4. Lecithin acts favorably on the saponification of the neutral fat. This is to be explained by the fact that the digestion of fat is accelerated by the presence of lecithin.

5. In spite of the lower lecithin content of the milk-yolk mixture the digestion of fat after taking said mixture was just as good as after the milk-lecithin mixture. The egg-yolk has this advantage because of the fineness of the emulsion and the chemical nature of fat contained in it.

6. It has been discovered that the passing of the milk fat from the stomach did not begin until the percentage content of fatty acids had about reached the maximum (2 hours after feeding). This percent of fatty acids was maintained almost unchanged during the further course of the digestion. Only during the last stages of the digestion does the percent of fatty acids rise again.

7. No lecithin was found in the intestine. It must, therefore, have been split either in the stomach or immediately after entrance into the intestine.

Lapidus (1910) announced results of preliminary experiments on the effect of lecithin on animal diastases. Lecithin in certain concentrations affected unfavorably the activity of salivary, pancreatic, serum and intestinal diastases in water and glycerin extracts, but activated serum diastase in ether solution.

Bickel (1911) suggests an indirect influence of the lecithin, leading to the better digestion and use of phosphorus from other parts of the diet.

Minami (1912) found that lipoids are superfluous for diastatic action by saliva.

Summary. As a result of these investigations we conclude that under certain experimental conditions, at least, lecithin may assist not only in the solution of fats and soaps, but also may accelerate the pancreatic cleavage of fats, and even the peptic digestion of casein. These actions vary much with the particular nutrient compounds involved, and with the experimental conditions, especially as regards concentration of the lecithin solution. At certain concentrations there may be acceleration of digestion, and at others a retarding action.

In the actual digestion of food within the alimentary tract lecithin seems to accelerate the digestion of fat, and also the passage of food from the stomach.

DIGESTION OF LECITHIN AND GLYCEROPHOSPHATES

That the digestion of lecithin may involve its cleavage has been observed by a considerable number of workers, among the earlier ones being Bókay (1877), who concluded from artificial digestion experiments and from feeding experiments with dogs, that lecithin is split in digestion by the fat-splitting ferment of the pancreas, or by putrefactive ferments in the intestine; and Hasebroek (1888), who concluded, from fermentation experiments, that the phosphorus from lecithin must be absorbed as glycerophosphoric acid; also Nesbitt (1899a, 1899b), who demonstrated the presence in the intestine of the dog of choline, neurine and an unidentified ptomaine after the ingestion of egg yolk and the occlusion of the small intestine at its lower end. See also Gaston (1902). Among the later workers to demonstrate the digestive cleavage of lecithin are Rogoziński (1910), Usuki (1910), and Yoshimoto (1910).

The cleavage products, as a rule, are choline, fatty acids and glycerophosphoric acid, but, according to J. and W. Cronheim (1911), the decomposition may go only to distearyl-phosphoric acid. The phosphorus of lecithin, then, is absorbed, in the main, in the same form as though ingested as glycerophosphate. That a portion of the lecithin is absorbed without cleavage, however, has been demonstrated by Slowtzoff, and others, as will be mentioned at greater length below.

Marfori (1905) studied the elimination of glycerophosphoric acid ingested by dogs and men. In men it was found, if administered in suitable amounts, to be absorbed from the alimentary canal. In dogs it is largely, though not completely, absorbed, a part being decomposed in the alimentary tract. At all events it is an easily assimilable compound.

Paul Mayer (1905) finds that the lipase of intestinal juice splits lecithin (racemic) asymmetrically; the dextro-lecithin is then decomposed, and the laevo-lecithin is not. From artificial digestion tests of lecithin with lipase (1906b), and from a study of the racemic and the laevo- forms as to optical activity, structure and cleavage products, the author concludes as reported above. The breakdown of the dextro-lecithin results in fatty acids and dextro-glycerophosphoric acid. It is suggested that the asymmetric cleavage, and difference in digestibility of the fractions, may have practical significance; since the various lecithin products used medicinally do differ in optical activity, that is, are more or less strongly racemized, it cannot be thought surprising that the results of lecithin therapy are very unequal, considering the different reactions of the enzymes on dextro- and laevo-lecithin.

Kutscher and Lohmann (1903) found that the ferment of the pancreas caused lecithin to break down into glycerophosphoric acid, fatty acids and neurine. Very little lecithin was decomposed by the gastric enzyme.

Stassano and Billon (1903a) concluded from microscopic examination that pancreatic juice does not cleave lecithin, and after feeding pure lecithin and egg yolk (1903b), and then examining the chyle with a polarizing microscope, they concluded that lecithin, taken pure,—not in albuminoid combination—escapes the digestive juices; and enters the circulation by way of the chyle unaltered.

Coriat (1904a) found that neither trypsin nor pepsin can split lecithin, but that lipase is able to do so. Pepsin and trypsin seem even to inhibit the normal enzymatic autolysis of brain tissue through which choline is liberated. Coriat finds that this autolytic enzyme acts only in neutral or slightly alkaline media, that the production of choline is greater in the latter than in the former, that the enzyme is inactive in slightly acid media, and that this enzyme can be destroyed by heat.

Slowtzoff (1906a) finds that lecithin given *per os* acts the same as lecithin given hypodermically, but that more must be given to produce the same result.

In eight experiments dogs were given egg yolk or lecithin, and the lymph was collected for analysis after 4-5 hours; also in four

experiments the intestinal contents of a dog, after it had ingested lecithin, were analyzed for lecithin and its splitting products; further, digestion experiments were conducted with lecithalbumin, and with digestive ferments *in vitro*.

Slowtzoff determined that lecithin in appreciable quantities reaches the blood unchanged, as well as in a saponified condition, by way of the chyle, but not by the portal vein; that lecithin may be saponified by the pancreatic juice, or even by steapsin; that the cleavage of lecithin to glycerophosphoric acid and choline occurs only in the duodenum; that pepsin-hydrochloric acid digestion does not affect lecithin, but that lecithalbumins are digested, the acid-albumin first formed being combined with the lecithin, in which form lecithin may perhaps be absorbed; the albumose solution resulting from pepsin digestion being free from lecithin. This lecith-acid albumin, when introduced *per rectum*, disappears.

Long (1906b) finds ether-soluble phosphorus in human feces equivalent to 1-5.5 gm. of lecithin per day. He quotes Deucher as finding in the feces of a man with closed pancreatic duct as high as 8 grams of lecithin per day. Long and Johnson (1906) suggest that feces lecithins may be but remotely related to simple distearyl lecithin, and also suggest that the feces lecithin may come in part each from food, intestinal epithelium, bile residues and bacteria.

Schumoff-Simanowski and Sieber (1906) state that lecithin (from egg yolk, and Kahlbaum's) is split by steapsin from the pancreas and from the stomach, more energetically by the former. Plant ferments, in particular that from the seeds of castor-oil plant, break it up also, and in the same way, by splitting off fatty acids. The lipase of blood of different animals does not cleave it.

Hamill (1906-7) determined by collection and analysis of chyle from a fistula in the thigh that lecithin administered by the mouth produced a rise in the ether-soluble phosphorus of the chyle.

Franchini (1907,1908a) sought to determine the fate of that portion of ingested lecithin which is absorbed without cleavage. By analysis of the bodies of rabbits after the feeding of lecithin he found a distinct rise of the lecithin content of both liver and muscle, but not of brain, following the ingestion of lecithin either during feeding or fast. There was also perhaps a slight increase of lecithin phosphorus in the excreta. No choline was found in the urine, but formic acid from the cleavage and oxidation of choline is said to have been present.

Marfori (1908b) in discussing the assimilation of organic phosphorus compounds says:

"Phosphorus in the form of synthetic glycerophosphoric acid, taken into the body by the mouth, is easily absorbed and assimilated. Lecithin administered either *per os* or subcutaneously is taken up at once by the tissues for their growth."

Clementi (1910) finds that pancreatic juice hydrolyzes the fatty acid radicals in lecithin; an action, however, which is not equally noticeable with all pancreatic juices, but which varies, in a more or less pronounced way, according to the capacity of the juices to saponify the ordinary glycerides. Intestinal juice lipase, as well as pancreatic juice lipase, acts on lecithin.

Mathison (1910) found synthetic glycerophosphoric acid not decomposed by pepsin, or trypsin, or by fresh pancreatic juice, either with or without enterokinase. He thinks, therefore, that glycerophosphoric acid is absorbed as such, though he notes the possibility that the natural and the artificial products may behave differently in this matter.

Brugsch and Masuda (1911) report that the intestinal juice contains a lecithin-cleaving ferment, and also that extracts of the colon bacillus and Staphylococcus cleave lecithin.

Grosser and Husler (1912) determined that the mucous membrane of the intestine, and the cells of the kidney, contain a ferment which completely splits glycerophosphate solutions. The lungs also contain such a ferment, but apparently in smaller amount. The liver and spleen show its presence but sparingly, while pancreas, muscle, heart muscle and blood are free from such a ferment. The feces contain this enzyme but the urine does not. Sodium glycerophosphate and the glycerophosphoric acid from natural lecithin were alike decomposed by this enzyme.

Ehrmann and Kruspe (1913) determined that the exclusion of bile from the alimentary tract greatly lowers the absorption of lecithin or causes its elimination in considerable quantity in the feces; and the exclusion of the pancreatic secretion produces a similar though less pronounced effect. These authors conclude that the total lecithin is not split by the pancreatic juice, but that a portion is absorbed as such. See also Forbes and associates (1914) under Nutr. Val. Org. and Inorg. P.

Summary. From the above investigations we conclude that lecithin is absorbed in part without digestive cleavage, in part after separation into choline, fatty acids and glycerophosphoric acid, probably in part combined as lecith-acid albumin, and probably also in part after the splitting of the glycerophosphoric acid to glycerin and inorganic phosphoric acid.

The digestive cleavage of lecithin is accomplished by the fat-splitting enzymes of the digestive tract, mostly in the duodenum.

Lecithin, as such, reaches the circulation by way of the chyle, but not by the portal vein.

The feces lecithin probably comes in part each from food, intestinal epithelium, bile residues and bacteria.

Lecithin taken by the mouth, or hypodermically, may be assimilated at once by the tissues.

Glycerophosphates are absorbed in part as such, and in part after cleavage to glycerin and inorganic phosphates.

BALANCE EXPERIMENTS WITH LECITHIN AND OTHER COMPOUNDS OF GLYCEROPHOSPHORIC ACID

Of the many observations on the nutritive value of compounds of glycerophosphoric acid comparatively few are of the nature of complete balance experiments. Additional evidence of this sort, especially comparing these with other phosphorus compounds, would be of value.

That the phosphorus of glycerophosphates is absorbed and retained is universally admitted. An experiment demonstrating this point is that of Sanson (1896), who fed calcium glycerophosphate to rabbits.

Considerable interest has attached to the function of lecithin in infant nutrition, especially as added to the milk in the form of egg yolk. Cronheim and Müller (1900) compared egg yolk and milk powder as elements in the diet of a child eleven and a half months old. The ration containing the egg yolk was rich in lecithin; the other was poor in lecithin. The calorific value of the latter was a trifle higher than that of the former. Nitrogen and phosphorus retention, and gain in weight all showed the ration containing the egg yolk to be the more efficient.

In a later series of experiments Cronheim and Müller (1902) made further comparisons of protein phosphorus and lecithin phosphorus in metabolism experiments with children, dogs and guinea pigs. The periods with children averaged four days in length, which is insufficient for mineral balance experiments. The results on infants are inconclusive.

Five young dogs were fed on similar rations to those received by the children. Egg yolk was compared with plasmon—a milk albumin preparation. These dogs were fed for 3 months, after which they were killed, and the bones subjected to study. The egg yolk had produced better bone development, and the marrow produced

by the ration containing this food was yellow and rich in fat, while that from the bones of the dogs which had received plasmon was red and immature.

Egg yolk and plasmon were also compared, using guinea pigs as subjects. The animals receiving the egg yolk grew the more rapidly and had the fatter livers.

Cronheim and Müller conclude that egg yolk, apparently through its lecithin content, especially favors nitrogen retention, and is to be recommended for use in the early feeding of the child.

Zuntz (1900) also conducted an experiment in infant metabolism in which a child, eleven and a half months old, was fed for two days on a milk diet in which 6 percent of the dry matter was replaced by egg yolk, followed by a period of the same length on milk alone. While receiving the egg yolk the child retained 24.2 percent of the nitrogen of the ration; on the milk diet the nitrogen retention was 9.9 percent of the intake; of the phosphorus of the egg ration 33.3 percent was retained, and of the diet of milk alone 17.4 percent was retained.

Lebbin (1901) conducted a 2-day metabolism experiment on a man 28 years old, and weighing 65 kg., using eggs, of which 22 were consumed, as the only food. The intake contained 286.28 gm. dry matter, and the outgo 14.28 gm. The eggs contained 39.22 gm. lecithin, and the excreta 3.517 gm.

Massacin (1902) conducted a series of balance experiments with a man suffering from pulmonary catarrh, on a normal mixed diet with lecithin added in certain periods. The addition of lecithin seems to have increased nitrogen retention.

Gilbert and Posternak (1903) conducted a balance experiment on a man, for the purpose of learning the effect of lecithin ingestion on phosphorus metabolism. The results are as stated below.

AVERAGE DAILY NITROGEN AND PHOSPHORUS BALANCES WITH A MAN ON DIETS WITH DIFFERENT LECITHIN CONTENTS—Grams

Nitrogen				Phosphorus (P_2O_5)				
Food	Urine	Feces	Balance	Food	Urine	Feces	Balance	
17.96	15.717	2.173	+0.07	2.430	1.840	0.603	−0.013	3-day preliminary period.
18.04	16.730	2.187	−0.88	2.745	2.139	0.576	+0.031	3-day period; same diet as above plus 15 gm. lecithin (total).

Thus it appears that the ingestion of 15 gm. commercial lecithin in two days (as the authors state, though the length of the period seems to be three days) caused a change of phosphorus balance

from −0.013 gm. P_2O_5 to +0.031 gm. P_2O_5. At the same time the nitrogen balance changed in the opposite direction, that is, from a positive to a negative balance.

Büchmann (1904) conducted balance experiments with two human subjects, administering lecithin as egg yolk, and in the pure form. A part of the data are given below.

DAILY CALCIUM, MAGNESIUM AND PHOSPHORUS METABOLISM WITH ADULT HUMAN BEINGS AS AFFECTED BY INGESTION OF LECITHIN—Grams

Subject and period	Length of period in days	P_2O_5 intake Grams	P_2O_5, percent retained	CaO intake Grams	CaO, percent retained	MgO intake Grams	MgO, percent retained	Diet
A1	10	6.13	8.56	5.72	21.88	0.43	5.34	Without lecithin.
A2	7	7.06	21.83	3.30	7.26	0.30	15.08	With egg yolk.
A3	7	7.04	6.32	3.28	2.94	0.30	15.07	Egg yolk and lecithin.
B1	5	5.65	neg.	5.55	neg.	0.42	neg.	Without lecithin.
B2	5	7.66	20.37	4.27	31.71	0.33	61.25	With egg yolk.
B3	5	6.10	7.21	5.19	9.69	0.48	54.36	Without lecithin.
B4	4	4.35	0.69	2.72	7.74	0.44	43.27	With edestin.

Most of this evidence tends to sustain the idea that lecithin increases phosphorus retention, though the result in period A3 is negative.

Völtz (1905) showed in a series of balance experiments on nitrogen metabolism with a dog that in a ration of meat, rice, albumin and lard, the replacement of one-third of the albumin nitrogen by the same amount of lecithin nitrogen increased the nitrogen retention from 0.020 to 0.140 gm. per day.

Gumpert (1905) conducted balance experiments with sanatogen, a preparation of casein and sodium glycerophosphate, with results as on the following page. The subject in this investigation was an adult man.

The change in period 4 from meat to sanatogen, and in period 5 from sanatogen back to meat showed that it was possible with this preparation to decrease the loss of phosphorus and calcium existing during the meat periods.

Experiment 2 reports an attempt to learn the effects of overfeeding with sanatogen. By its use it was found possible to bring about a marked storage of both nitrogen and phosphorus, which fact gains added significance from the coincident loss in calcium. The plan of the experiment is such, however, that we are unable to judge of the participation of the glycerophosphoric acid of the sanatogen in the production of the results noted. The food in periods 2, 3 and 4 of Exp. 2 was essentially the same as in the meat periods of Exp. 1 except for the addition of 60 gm. of sanatogen.

As bearing on matters of general metabolism it is of interest that phosphorus may be stored in a grown man, in considerable quantity, for a number of days at least, irrespective of the calcium balance.

DAILY NITROGEN, PHOSPHORUS AND CALCIUM BALANCES ON DIETS CONTAINING DIFFERENT PHOSPHORUS COMPOUNDS

Grams

Exp. No.	Periods	Diet	N intake	N balance	P_2O_5 intake	P_2O_5 balance	CaO intake	CaO balance
I	1 4 days	Normal mixed + meat	11.6	+0.38	1.80	−0.404	0.265	−0.339
	2 5 days	Normal mixed + casein	11.6	+0.75	1.885	−0.018	0.367	−0.088
	3 3 days	Normal mixed + meat	11.6	+0.45	1.80	−0.252	0.265	−0.222
	4 5 days	Normal mixed + sanatogen	11.6	+0.54	2.877	−0.012	0.303	−0.182
	5 1 day	Normal mixed + meat	11.6	+0.81	1.80	−0.425	0.265	−0.313
II	1 4 days	Normal mixed	12.0	+1.34	1.90	−0.28	0.165	−0.265
	2 3 days	Normal mixed + sanatogen	19.87	+3.99	3.91	+0.552	0.216	−0.214
	3 3 days	Normal mixed + sanatogen	19.87	+2.04	3.91	+0.143	0.216	−0.307
	4 4 days	Normal mixed + sanatogen	19.87	+3.74	3.91	+0.600	0.216	−0.244

Slowtzoff (1906b) showed in three balance experiments with normal men, himself included, that the ingestion of lecithin caused nitrogen and phosphorus retention, and a decrease of urinary sulphur, all of which suggest protein synthesis.

According to Slowtzoff, Umikoff showed that the protein reserve is stored in the muscles and liver principally as myosin and myostromin (the phosphorus-containing proteins that remain in muscle after myosin extraction, and which in composition and solubility resemble the nucleoalbumins).

Slowtzoff found that 24 hours after the taking of food a transformation of the myosin into myostromin took place. Slowtzoff says that if his conclusions and those of Umikoff are correct we may consider the transformation of absorbed protein into the organized, as an enriching of absorbed protein with phosphoric acid and xanthin substances. Then the action of lecithin would be favorable for this organization, and it would be comprehensible that protein retention is accompanied by retention of xanthin and phosphoric acid.

Marfori (1908a, 1908b) concluded that the phosphorus of synthetic glycerophosphoric acid, if taken by the mouth, is easily absorbed and assimilated; that glycerophosphates introduced subcutaneously are not retained, but instead are quickly excreted by the kidneys; lecithin, on the other hand, Marfori found to be retained and assimilated whether introduced *per os* or subcutaneously.

Togami (1908) sought to determine with a growing dog whether or not ingestion of sodium glycerophosphate, by a healthy animal, would lead to increased phosphorus storage. In a preliminary period on meat alone the dog was storing phosphorus. Then during 6 days there was added to the meat diet, each day, 3.2291 gm. P_2O_5 in the form of sodium glycerophosphate. This change produced marked digestive disturbance, with vomiting on the third and fourth days. There was a marked increase in the urinary phosphorus, and a decrease in the phosphorus retention, though the phosphorus balance remained positive. In the after period of 6 days, on meat alone, the phosphorus balance was negative, the daily urinary phosphorus excretion showing a gradual elimination of accumulated phosphorus from the glycerophosphate.

There was, therefore, no evidence of permanent retention of phosphorus from the sodium glycerophosphate. Clearly it was not retained. One should bear in mind, however, that the poverty of the basal ration in calcium, and the fact that the glycerophosphate was fed as a sodium salt were conditions unfavorable for phosphorus retention.

J. and W. Cronheim (1910) studied phosphorus metabolism in infants, as affected by lecithin, which was used to replace such part of the milk as to leave the nitrogen and phosphorus of the milk plus lecithin as nearly as possible the same as of the diet of milk alone. With one child the lecithin increased the nitrogen retention from 2.69 percent of the intake to 4.44 percent of the same, and the phosphorus retention from a negative balance to a positive balance of 15.69 percent of the intake.

With a second child the nitrogen retention was reduced from 5.61 to 4.01 percent of the intake, and the phosphorus retention increased from 1.69 to 2.34 percent of the intake. Calcium retention was decreased in both cases. These results must be considered inconclusive.

Yoshimoto (1910) studied the effects of lecithin ingestion on protein metabolism in the dog. Lecithin was added to a basal ration of horse-flesh, bacon, salt and water. In the lecithin periods there was evidently a significant retention of both nitrogen and phosphorus, the effects continuing into the after-periods.

A. Loeb (1911) found in balance experiments with two human beings that the retention of lecithin phosphorus was not accompanied by such a decrease of calcium and phosphorus outgo as suggested deposition of the phosphorus in the bones, in fact the calcium outgo was increased. The balance periods were 3-5 days in length —insufficient for the purpose.

Bickel (1911a) conducted balance experiments with a man 26 years old and weighing about 66 kg., studying the influence of lecithin on metabolism. The following table we have calculated from the author's data:

AVERAGE DAILY NITROGEN AND PHOSPHORUS (P_2O_5) BALANCES WITH A MATURE MAN AS INFLUENCED BY LECITHIN—Grams

Periods	Nitrogen				Phosphorus (P_2O_5)				Diet
	Food	Urine	Feces	Balance	Food	Urine	Feces	Balance	
Fore-period 3 days	24.530	16.387	4.200	+3.943	7.880	4.200	1.633	+2.047	Normal mixed standard diet.
Main period 5 days	"	19.450	3.080	+2.000	9.160	4.638	2.260	+2.262	Same plus "biocitin."
After period 5 days	"	19.416	3.416	+1.698	7.880	3.996	2.014	+1.866	Standard diet plus dry egg white.
Fore-period 3 days	"	16.997	4.533	+3.000	7.880	3.713	1.257	+2.910	Standard diet plus dry egg white.
Main period 5 days	"	17.356	4.520	+2.654	8.400	3.814	1.280	+3.306	Standard diet, dry egg white and lecithin.
After period 5 days	"	17.444	4.404	+2.682	7.880	3.642	1.474	+2.764	Standard diet plus dry egg white

Lecithin fed in the pure form, or as "biocitin," was apparently absorbed and retained, at least the feeding of these preparations increased the phosphorus retention. The amounts of phosphorus ingested were about twice the maintenance requirement, and the phosphorus retention was remarkably large. See also Bickel (1911b).

Patta (1912) reports that, in doses of 0.50-0.75 gm. per day, lecithin manifests a sparing action toward the phosphorus and nitrogen balance of the body, this effect being most pronounced when there has been a negative balance during the period preceding the injection.

Satta and Gastoldi (1913) report that if animals are in nitrogen and phosphorus equilibrium they eliminate the phosphorus of lecithin principally as inorganic phosphate in the urine, and that if not in equilibrium phosphorus from the lecithin is retained.

Summary. The phosphorus of lecithin and glycerophosphates may be absorbed from the alimentary tract and utilized in the tissues. Lecithin administered subcutaneously may be retained, but there is some evidence that glycerophosphates, under this condition, are quickly eliminated by the kidneys.

Lecithin added in the form of egg yolk to the milk diet of an infant appears to favor nitrogen and phosphorus retention, and gain in weight.

Egg yolk as compared with plasmon—a milk albumin preparation—appeared, from experiments with dogs and guinea pigs, to favor the growth of the animal, and the development of the bones.

As with other phosphorus compounds lecithin and the glycerophosphates are, in their metabolism, largely independent of nitrogen and calcium, at least during the limited periods covered by most balance experiments.

We have in these balance data no evidence of the possession by lecithin or glycerophosphates of any unusual nutritive or stimulative values, when added to the normal food of healthy animals. That they do possess a higher degree of usefulness in states of impoverishment, however, seems probable. Naturally, the apparent results of the administration of these compounds depend on the nutritive status of the subject, and on the other dietetic treatments used for comparison. In some states of nutritive derangement they possess life-saving capacity; in some other more favorable circumstances they may be of no unusual value.

GROWTH AND COMPOSITION OF ANIMALS AS AFFECTED BY COMPOUNDS OF GLYCEROPHOSPHORIC ACID

Protracted experiments with glycerophosphoric acid compounds in the growth of animals have been prolific of results of interest, and there is considerable evidence of this nature which indicates at least a high degree of usefulness of these compounds in the animal economy, if indeed some of them are not essential to the maintenance of life.

Heffter (1891) shows that the lecithin of the liver is decreased by starvation and by phosphorus poisoning.

Umikoff (1895) experimented with rats and doves on rations containing various compounds of phosphorus. They throve only on rations containing lecithin.

Danielewsky (1895b) reared tadpoles in lecithin solutions, and reported marked increase in growth in excess of that made by the controls in water without lecithin. He ascribes to lecithin a marked stimulating influence on the processes of multiplication of cellular elements. Danielewsky's observations on the effects of lecithin on the growth of tadpoles have not been corroborated.

Danielewsky (1896) conducted injection and feeding experiments on chickens and young dogs with lecithin. In each case the animal receiving the lecithin made greater gain in weight than the control. The doses, given at intervals of 3-5 days, were about 5-10 mg. for the chicks, and 20-50 mg. for the pups. The dose was doubled or tripled when given by the mouth.

Danielewsky states that lecithin has a stimulating influence, doubtless in connection with the increase of erythrocytes and haemoglobin in the blood. Numerical data are given on page 297.

EFFECT OF LECITHIN ON THE GROWTH OF CHICKS AND YOUNG DOGS

Series	Animals	First weight Grams	Final weight Grams	Treatment	Time of experiment
I.	1	97	785	Lecithin	Aug. 26-Dec. 5
I.	2 (ave.)	99.5	746	Control	Aug. 26-Dec. 5
II.	2 (ave.)	249	1187	Lecithin	Sept. 28-Nov. 13
II.	1	264	880	Control	Sept. 28-Nov. 13
III.	1	495	4080	Lecithin	Aug. 25-Oct. 30
III.	1	560	3630	Control	Aug. 25-Oct. 30
IV.	1	746	4085	Lecithin	June 21-Nov. 28
IV.	1	679	2965	Control	June 21-Nov. 28
V.	1	495	7450	Lecithin	June 21-Oct. 18
V.	1	484	11170	Lecithin	June 21-Oct. 18
V.	1	459	7420	Control	June 21-Oct. 18
V.	1	487	6820	Control	June 21-Oct. 18
VI.	1	670	6570	Lecithin	Jan. 25-Apr. 17
VI.	1	720	5930	Control	Jan. 25-Apr. 17

Danielewsky (1897) submitted photographs showing lecithin-treated animals surpassing the controls by one-half or two-thirds in length. He also claims that the lecithin affects the psychic development of the young dogs in a remarkable manner.

Desgrez and Zaky (1900) injected subcutaneously into guinea pigs lecithin dissolved in sterile olive oil. The dose was 40-60 mg. per day during 8 or 10 days. The lecithin increased the urinary nitrogen, decreased the urinary phosphorus outgo, and increased the live weight as compared with controls. The apparent result, of course, depends on the treatment of the control.

Wildiers (1900) reports negative results from the feeding of lecithin to tadpoles, chickens and dogs. The metamorphosis of the tadpoles was delayed; no increased growth or increase of red blood corpuscles was produced by hypodermic injection of lecithin in an anaemic dog.

Carrière (1901) reports benefit from the use of lecithin with six normal children, during a period of six months. Data are submitted on height and weight before and after treatment; and statements are made as to results on blood and urine, but no data are included on feces or food. According to Carrière's observations the usual effects of lecithin to increase the urea and decrease the urinary phosphorus were at first apparent, but passed away by the end of the experiment. The red blood corpuscles are said also to have been increased by lecithin treatment.

Desgrez and Zaky (1901a, 1902a, 1902b, 1902c) conducted a series of studies on the influence of lecithin on the animal organism, especially on the live weight, the development of the skeleton and nervous tissue, and on the composition of the urine. The subjects were guinea pigs, rabbits and dogs. Egg-yolk lecithin was administered by the mouth, or subcutaneously. A part of the results are as follows:

1. Three lots of guinea pigs, 3 in each lot, were fed on bread, bran and cabbage; quantities not stated. One lot served as controls; a second received lecithin subcutaneously, and a third received lecithin in pills. In 43 days the controls gained 480 gm., those treated subcutaneously 670 gm. and those receiving lecithin *per os* 850 gm. The two lots receiving lecithin excreted more urinary nitrogen, but less urinary phosphorus than the controls.

2. Two guinea pigs from the same litter were used as the subjects of a similar experiment; one was used as a control, and the other was injected with lecithin. In one month the control gained in weight 120 gm.; the injected one 240 gm.

3. Of three dogs from the same litter one was used as a control; one was injected subcutaneously, and the third received the same amount of lecithin in the form of pills. In 27 days the control gained 1480 gm., the injected dog 2050 gm. and the one receiving lecithin *per os* 2100 gm. The dogs receiving lecithin excreted more nitrogen, but less phosphorus than the control.

4. During inanition it was found with guinea pigs that those injected with lecithin in olive oil lived longer than those injected with olive oil alone.

5. After 60 days treatment as under (1) it was found, by killing the guinea pigs, that both the absolute and relative weight of the brains of the treated guinea pigs were greater than the controls, while the weight of the femora of the treated animals exceeded the controls only in the case of those which had received lecithin by the mouth.

6. After 7 months' treatment as under (2), the control and the treated animals compared as follows: live weight, 750 gm.:830 gm.; weight of brain, 2.08 gm.:2.24 gm.; weight of left femur, 1.28 gm.:1.60 gm.

7. Five guinea pigs were used as controls while five others received lecithin by the mouth, from Nov. 1 to Dec. 24. All were killed on Jan. 6 and 7. The controls and the treated animals compared as follows: live weight, 2510 gm.:2840 gm.; gain in body weight, 780 gm.:1200 gm.; brain, 16.56 gm.:18.14 gm.; left femur, 6.16 gm.:6.65 gm.; phosphorus per 100 gm. of brain, 0.358 gm.:0.373 gm.; lecithin per 100 gm. of brain, 4.03 gm.:4.19 gm.; mineral matter per 100 gm. of femur, 66.80 gm.:69.30 gm.; P_2O_5 per 100 gm. mineral matter, 39.68 gm.:41.52 gm.

8. Of 2 rabbits one was used as a control, and the other received daily 0.10 gm. lecithin by the mouth. During 40 days the control gained 200 gm., and the other 350 gm. in live weight. The control and the lecithin rabbit compared as follows: live weight,

2020 gm.:2200 gm.; weight of brain, 8.18 gm.:9.28 gm.; weight of femur, 8.26 gm.:8.59 gm.; total phosphorus per 100 gm. of brain, 0.341 gm.:0.367 gm.; mineral matter per 100 gm. femur, 61.74 gm.: 62.20 gm.; P_2O_5 per 100 gm. mineral matter of femur, 38.01 gm.: 39.91 gm.

9. Of two rabbits from the same litter, one was used as a control, and the other received 0.10 gm. lecithin daily for two and a half months. The control and the lecithin rabbit compared as follows: live weight, 2450 gm.:2170 gm.; gain in weight, 760 gm.:890 gm.; brain, 8.92 gm.:9.11 gm.; femur, 10.14 gm.:8.28 gm.; phosphorus per 100 gm. brain, 0.356 gm.:0.347 gm.; mineral matter per 100 gm. femur, 65.10 gm.:66.94 gm.; P_2O_5 per 100 gm. mineral matter of femur, 37.17 gm.:39.71 gm.

10. Of two dogs of the same age, one was used as a control, and the other received 0.10 gm. lecithin per day from Oct. 1 to Dec. 6. The control and the lecithin dog compared as follows: live weight, 2550 gm.:3780 gm.; gain in weight, 300 gm.:1380 gm.; weight of brain, 46.42 gm.;49.90 gm.; weight of femur, 10.27 gm.:11.00 gm.; phosphorus per 100 gm. of brain, 0.365 gm.:0.397 gm.; lecithin per 100 gm. of brain, 3.73 gm.:4.06 gm.; mineral matter per 100 gm. femur, 61.03 gm.:62.81 gm.; P_2O_5 per 100 gm. mineral matter in femur, 38.9 gm.:37.86 gm.

11. Of two dogs of the same litter, one was used as a control, while the other received daily for two months 0.10 gm. lecithin. Three months later the dogs were killed. The control and the lecithin dog compared as follows: live weight, 13300 gm.:13340 gm.; weight of brain, 69 gm.:76 gm.; weight of femur, 59 gm.:68 gm.; phosphorus per 100 gm. brain, 0.357 gm.:0.340 gm.; lecithin per 100 gm. brain, 3.82 gm.: 3.97 gm.; mineral matter per 100 gm. femur, 62.40 gm.:65.14 gm.; P_2O_5 per 100 gm. mineral matter in femur, 39.07 gm.:39.82 gm.

12. In analyzing the mode of action of lecithin, Desgrez and Zaky found with guinea pigs that sodium glycerophosphate increased the urinary nitrogen, but did not alter the phosphorus outgo. Choline, however, subcutaneously injected in quantities of 1 c.c. of a 2-percent solution during 8 months, decreased the urinary phosphorus, and increased the live weight. Betain also decreased the urinary phosphorus, but caused loss in live weight.

A part of the author's conclusions are as follows:

Lecithin of egg exercises on the nutritive exchanges a favorable influence which is manifested by an increase in the urea, the total nitrogen, and the nitrogen coëfficient. There is at the same time a constant decrease in the amount of phosphoric acid eliminated through the urine. The appetite and weight of the animals in-

Lecithin administered to guinea pigs in a state of inanition prolongs life some days. The loss of weight at the time of death is practically equal in both control and treated animals; the proportion of material utilized is the same; the process of nutrition being better in the treated animals, they survive longer, because of a more perfect elaboration of their reserves and of the protein of their tissues.

The increase in weight of the treated animals does not mean an increase in fatty tissue. It takes place proportionately in the skeleton and the nervous system. In the skeleton it results in an increasing of the mineral material, particularly of phosphoric acid; in the nervous system, an increase in total phosphorus and in lecithin.

Springer (1902) reports lecithin injection and feeding experiments with guinea pigs, rabbits and dogs. The results were inconclusive as to effects on weight of brain per unit of body weight, and also on weight and length of bones. The total phosphorus and the lecithin of the brain, and the mineral matter of the bone were in each case greater where lecithin had been administered than in the controls. A part of the figures are as follows:

EFFECTS OF LECITHIN ON THE COMPOSITION OF THE BRAIN AND BONES OF ANIMALS

Experiment and subject	Method of administration of lecithin	Percent phosphorus (P_2O_5) in brain	Percent lecithin in brain	Percent mineral matter in femur	Percent P_2O_5 in mineral matter of femur
II Guinea pigs....	Controls (5) 0.05 gm. in food daily	0.358 0.373	4.03 4.19	66.80 69.30	39.68 41.52
III Rabbits.....	Control (1) 0.100 gm. daily in food	0.341 0.367		61.74 66.20	38.01 39.91
IV Dogs.	Control (1) 0 100 gm. daily in food	0.365 0.397	3.73 4.06	61 03 62.81	38.90 37.86

Hatai (1903) conducted feeding and injection experiments with lecithin on white rats. The treated animals in each of 5 cases gained more in weight than the controls, though the amounts of food consumed were not stated. The relative weight of the central nervous system of the lecithin rats was normal, as was also its moisture content and the relative development of sheath and axis cylinder.

Lusena (1903) determined that the lecithin content of the liver, kidneys and myocardium under acute poisoning by arsenic and by phosphorus did not vary much from the normal, and concluded (a) that in experimental fatty degeneration the larger part of the fat in the degenerated organs is infiltrated fat, (b) that it is not dis-

proved that a part of the fat is of endocellular origin, from the transformation of protein, and (c) that though the protein may change to fat, the lecithin is not the transformation substance, for the lecithin is present within normal variations both in cloudy swelling and advanced fatty degeneration. See also Billon and Stassano (1903a, 1903b).

Dorn (1904) conducted feeding experiments with rabbits showing the nutritive value of lecithin and protylin. Protylin is recommended for use in scrofula, anaemia and rachitis.

Desgrez and Zaky (1904a, 1904b, 1904c, 1905) compared lecithin, protylin, nuclein (from yeast), and nucleic acid (also from yeast), as to their influence on the development and composition of animals. The subjects were dogs and guinea pigs, and the program included feeding experiments, with some metabolism data, and partial body analyses.

All of these organic phosphorus compounds were found to be of value in causing increase in weight greater than that of the controls. The brain increased in weight, as did the bones; and the bones increased in ash under the influence of these compounds. The authors considered lecithin and protylin to be more valuable, and nucleic acid less valuable than the other compounds in causing gain in live weight. Since there were no feces phosphorus figures we have no basis for a critical judgment of their conclusions.

Pignatti (1906) studied the influence of oral or subcutaneous introduction of various organic phosphorus compounds on the ferratin in the liver. Casein, sodium glycerophosphate, and lecithin increased the ferratin of the liver. It was further concluded that by injection of the glycerophosphate the phosphorus content of ferratin is not increased, but that casein injection does give a ferratin possessing a high phosphorus content.

Morgen, Beger and Fingerling (1906) report results of sheep and goat feeding experiments, with lecithin, as affecting milk production, which seem to show that in doses of 1-2 gm. this compound increases the secretion of milk and milk solids, fat production, however, being increased only when the basal ration was low in fat.

Goldfarb (1907) studied the effects of lecithin on growth with tadpoles and kittens. The tadpoles were kept in lecithin solutions of various strength, from one one-hundred-fiftieth to two percent. The kittens received lecithin subcutaneously, or in the food. The tadpoles so treated showed no greater increase in weight than the controls. The kittens which received the lecithin gained, on an average, about 7 percent more than the controls.

In a later series of experiments (1910) similar negative results were obtained with tadpoles and sea-urchin eggs, also in lecithin solution; with an experiment involving 52 kittens, those receiving lecithin did not, on the whole, exceed in growth those not receiving lecithin. An experiment on a litter of 5 guinea pigs also gave negative results.

Franchini (1907, 1908a) investigated the question of method of utilization of lecithin by the animal organism, in experiments on rabbits. Two lots of seven rabbits each were used. During three days each rabbit of one lot received 4.799 gm. of pure lecithin, but no other food. The other lot received neither lecithin nor food. Both lots received water to drink. Both lots were killed four days after the beginning of the treatment, twenty-four hours after the last feeding of lecithin.

The lecithin feeding increased the lecithin content of the liver and muscle, but not of the brain. Franchini accepts Slowtzoff's conclusion that lecithin, in part at least, is absorbed as such, unsplit.

Forbes (1909) compared lecithin with other organic and inorganic phosphorus compounds in the growth of swine. Results on more individuals will be necessary to settle many of the points of interest, but the observed effects of lecithin on the composition of the muscles is considered characteristic. The moisture content of the fat-free muscle was higher than in any other lot, as also was the total phosphorus, either as related to the whole meat, the protein or the ash. See also Forbes (1909); Common Foods in Rel. to P. Met. and Forbes and associates (1914); Nutr. Val. Org. and Inorg. P.

W. Cronheim (1912) conducted metabolism experiments, with two mature men on rations varying in lecithin content, from which he concluded that for grown people as well as children lecithin is an important constituent of the diet, and that it has the same value for adults as has often been observed for children, in favoring the replacement of lost nitrogenous material.

Wesselkin (1913) made a microchemical study, with rabbits as subjects, of the fatty bodies deposited in the organs as a result of the feeding of lecithin and of egg yolk. Both forms of nutriment caused a deposit of lipoid substances other than true fats. Among these substances were phosphatids and apparently lecithin. The phosphatid formed as a result of the yolk feeding was much in excess of the amount stored as a result of the feeding of the same amount of lecithin in the pure form. The lipoids resulting from feeding egg yolk were mainly cholesterin esters.

Salkowski (1913b) reports an increase of the phosphorus of the brain through the administration of cephalin in pill form to fasting rabbits during four-day periods. It is Salkowski's idea that cephalin is stored in the brain. The extent of the work was insufficient to establish so important a point.

Summary. In all such experiments as the above the results depend on the comparison of the experimental animals with the controls, that is, of the animals receiving the nutrients of interest, with others not receiving them. It is, therefore, obvious that the status of the controls has as much to do with apparent results as does the behavior of the animals receiving the nutrients in question.

It is our own belief, therefore, that some at least of the differences in the conclusions of the different investigators are due to differences in the conditions attending the experiments, especially in the state of nutrition of the animals, and their susceptibility to the effects of the experimental treatment, as determined by previous conditions of life. It would therefore be desirable that we know much more than has been recorded in regard to some of the conditions which affect results, but which are not commonly recognized as of importance.

From the investigations above mentioned one must conclude that whatever the function of lecithin and related compounds in the normal life of animals there are conditions not definitely distinct from the normal in which they do possess certain important specific effects.

In comparison with more or less carefully chosen controls, animals receiving lecithin, especially if the basal ration be low in phosphorus, and the animals in a state of depleted reserves, show increased appetite and gain in live weight; phosphorus retention is favored; there has been observed an increase of ash and of phosphorus in the skeleton, and of phosphorus in the muscles, and of phosphorus and lecithin in the brain; fasting animals live longer if they receive lecithin, and their livers and muscles are increased in lecithin content by ingestion of lecithin. See also Lecithin Therapy.

METABOLISM OF PHOSPHOCARNIC ACID

Siegfried (1894, 1895, 1896) argues that since phosphocarnic acid contains both phosphorus and iron, and readily forms easily soluble compounds with lime and magnesia, and since these compounds are soluble in either neutral, weakly acid or weakly alkaline solutions it is fitted to serve as a carrier of phosphorus, iron, lime and

magnesia throughout the body fluids. Its presence in considerable quantity in milk is in harmony with this view. Taken in meat or its extractives it can render available the lime either of other foods or of drinking water.

Siegfried performed experiments on dogs in a study of the relation of phosphocarnic acid to muscular work. A nerve in one hind leg was cut; then the corresponding muscle of the other hind leg was stimulated to activity for one hour by an electric current. The dog was then killed, and phosphocarnic acid determined in the fresh and in the tired muscle. The tired muscle always showed less phosphocarnic acid than the rested one, at one time reaching a ratio of 1:3. Siegfried suggests that the phosphocarnic acid of muscle is an energy-producing nutrient rather than a metabolic waste product.

In the latest experiments described the ischiatic and crural nerves were severed, and then stimulated by an induction current, causing tetanus alternately in the flexor and extensor muscles. After 1 hour and 50 minutes the dog was killed and the flexors and extensors of both thighs were removed and examined. In a second experiment the same nerves were severed, and, after the healing of the wound the dog was exercised rapidly for 1 hour and 15 minutes; then killed, and the muscles examined. A third experiment, similar to the second was conducted, the time of exercise being 1 hour and 30 minutes. Below are the numerical results.

PHOSPHOCARNIC ACID IN TIRED AND RESTED MUSCLES—Grams

	Weight of muscle		Absolute weight of phosphocarnic acid (reckoned as carnic)		Phosphocarnic acid in 1000 gm. muscle		Phosphocarnic acid used for the muscular work	
	Rested	Tired	Rested	Tired	Rested	Tired	Per 1000 gm. muscle	Per 100 parts phospho-carnic acid
I.....	645	640	1.6193	0.5996	2.40	0.93	1.47	61.3
II.....	845	1010	1.1116	0.7344	1.31	0.73	0.58	44.3
III.....	955	1210	0.5463	0.4697	0.57	0.39	0.18	31.6

The work of Macleod does not sustain Siegfried's theory. See Macleod (1899), Effects of Exercise on P. Met.

Martin Müller (1897) found very much lower values for phosphocarnic acid in the muscle in new-born infants than in adults.

Tarozzi's observations (1899a, 1899b) do not indicate any change in the proportion of phosphocarnic acid in striated muscle during fast. See table on next page.

Bonanni (1902) found that the phosphocarnic acid of the muscles of rabbits in acute veratrum poisoning was reduced from the normal 1.819 percent (mean of 3 determinations) to 1.426 percent (mean of 4 determinations).

Cavazzani (1904a) studied the phosphocarnic acid content of the brains of dogs after different degrees of nervous excitement. Those killed immediately after morphine sleep showed 0.217—0.285 percent ferrinucleon, with 6.61—7.04 percent nitrogen, and those killed after absynth excitement showed 0.543—0.690 percent ferrinucleon, with 3.24—5.74 percent nitrogen.

PHOSPHOCARNIC ACID OF MUSCLES FROM NORMAL AND FASTED DOGS (Tarozzi, 1899)

Condition of dog	Duration of fast	Loss of weight	Mass of muscle	Carnic acid	
	Days	Percent	Grams	In toto	Parts per 1000
Normal	..	..	400	0.618	1.545
Normal	..	..	450	0.6282	1.396
Normal	..	..	320	0.5728	1.790
Fasted	6	10	435	0.607	1.580
Fasted	28	28	595	0.787	1.324
Fasted	50	45	442	0.804	1.818

Panella (1906a) found that the quantity of phosphocarnic acid in the brain (dog) gradually fell off during fast, the decrease being in direct proportion to the duration of the fast. The same was true independent of the water content, which increased during the fast when water but no food was taken.

METABOLISM OF PHYTIN

FEEDING EXPERIMENTS WITH MEN AND ANIMALS

As one of the most important organic phosphorus compounds in foods of vegetable origin, and as that one which contains much the highest percentage of phosphorus, especial attention attaches to the metabolism of phytin. A considerable amount of careful work has been done on phytin within the past few years, and its status as a nutrient is fairly well established.

Scofone (1904) found that phytin phosphorus is mostly absorbed, and is excreted largely by the kidneys, as inorganic phosphate.

Giacosa (1904) fed phytin to a dog. The phosphorus of both urine and feces was increased, the inorganic phosphorus of the feces being increased more than the organic. In administering phytin to human beings (1905), in 10 gm. doses, no evidence was noted of urinary elimination of either phytin or inosite. The relation of phytin to glycogen was studied by introducing phytin into the stomach of starving dogs and rabbits. The animals which received the phytin lost the most in weight, and their livers contained, as a rule, less glycogen. Giacosa (1907) found the mortal dose much less when injected than when taken by the mouth.

Maëstro (1905b) presented balance data with rabbits showing that phytin phosphorus is absorbed, and may be retained.

Gilbert and Posternak (1905) reported a balance experiment on a man, in an overfed condition, showing that the addition of phytin to the food increased the phosphorus but decreased the nitrogen retention. Data on this test are given below.

AVERAGE DAILY PHOSPHORUS METABOLISM WITH A MAN IN AN OVERFED CONDITION AS AFFECTED BY PHYTIN
Periods of Five Days—Grams

Remarks	Nitrogen				P_2O_5			
	Food	Urine	Feces	Balance	Food	Urine	Feces	Balance
Fore-period	22.73	19.01	1.69	+2.03	3.68	2.721	0.924	+0.039
Diet same as above plus 0.6 gm. P_2O_5 daily as phytin	22.73	20.93	1.51	+0.29	4.28	2.960	1.262	+0.062

In another experiment these authors compared phytin phosphorus with other compounds (see Nutr. Val. Org. and Inorg. P.); but the amounts fed were not nearly enough the same to warrant conclusions other than that the phytin phosphorus was absorbed and retained, but, as before, without beneficial effect on the nitrogen balance, which remained negative.

Jordan, Hart and Patten (1906) conducted phosphorus metabolism experiments on two milch cows, one animal being used for Experiment I and the other for Experiments II and III. The phosphorus contents of the rations were varied by choice of food and by method of preparation, as in the washing of bran to remove soluble phosphorus compounds. The cows were kept in a warmed room and the excreta were caught by attendants. The cows were milked at 7 a. m., noon, five P. M., and midnight. Inorganic phosphorus was determined by the method of Hart and Andrews. Nuclein and nucleo-proteid phosphorus were estimated as that portion of the total phosphorus which was insoluble during a 15-minute extraction with 0.2 percent hydrochloric acid. Soluble organic phosphorus is considered to be the total dissolved by 0.2 percent hydrochloric acid minus the inorganic phosphorus as determined by the Hart and Andrews method.

Among the authors' conclusions are the following:

The amount of outgoing phosphorus rose and fell with the quantity supplied in the food, though within narrower limits. When the phosphorus supply was abundant, there was a storage of this

element in the bodies of the animals, but during prolonged periods, in which the phosphorus supply was deficient, there was withdrawn from the body store about 10 gm. daily.

Through katabolic changes the phosphorus of the phytin and that of the unused digested nucleo-bodies was reduced to inorganic combinations, and was excreted, chiefly in the feces, though to a small extent in the urine. ' The inorganic phosphates of the milk were from three to five times greater in quantity than the total amount of such compounds in the food.

The rise and fall in the amounts of outgoing phosphorus compounds occurred almost wholly with the inorganic salts found in the egesta. The organic phosphorus bodies of the egesta were but little affected, if at all, by the proportions of phosphorus compounds in the food. Variations in the phosphorus supply appeared not to modify the appropriation of this element by the milk.

No relation whatever appears to exist between the nitrogen excretion and the phosphorus excretion.

It was shown, without question, that the physiological effect of the two rations, due to the withdrawal from the bran of such compounds as were soluble in slightly acidulated water, differed to a marked degree. With the washed-bran ration as compared with the one containing the unwashed bran, the following differences were observed:

a. Drier and much firmer feces with the washed-bran ration.

b. A greatly reduced flow of urine following a change from the unwashed-bran to the washed-bran ration, the reverse taking place when a reverse change was made.

c. An increase in the flow of milk consequent upon the withdrawal from the ration of the phytin and other water-soluble constituents of bran.

d. A reduction, sometimes large, in the percentage of fat in the milk consequent upon the withdrawal from the ration of phytin and other water-soluble constituents of bran.

e. A decreased production of butter fat during the period in which the washed-bran ration was fed, notwithstanding a somewhat increased flow of milk.

The following tables set forth some of the main points in this work.

DAILY PHOSPHORUS METABOLISM WITH MILCH COWS

EXPERIMENT I

Dates	Total P fed	Daily income and outgo					Rations
		Fed	Outgo	Feces	Milk	Urine	
Total Phosphorus							
Mar. 10-Mar. 16		12.8	22.7	8.40	14.2	0.10	No. 1 Oat straw 10 lbs., washed bran 10 lbs., rice 6 lbs., wheat gluten 1.5 lbs.
Apr. 12-Apr. 18		78.7	70.6	55.70	11.0	3.90	No. 2 Oat straw 10 lbs., whole bran 10 lbs., hominy feed 5 lbs., wheat gluten 1 lb.
Apr. 28-May 1		16.0	23.8	13.29	10.1	0.37	No. 1 Low phytin and nuclein ration.
May 9-May 15		83.3	70.4	56.70	8.8	4.88	No. 2 High " " " "
May 22-May 26		21.4	22.7	9.59	13.0	0.11	No. 1 Low " " " "
June 10-June 16		15.1	20.5	9.40	11.0	0.12	No. 1 Low " " " "
Nucleo-phosphorus							
Mar. 10-Mar. 16	12.8	7.6	6.6	3.9	2.6	0.00	No. 1 Low " " " "
Apr. 12-Apr. 18	78.7	24.4	9.5	7.6	1.9	0.00	No. 2 High " " " "
Apr. 28-May 1	16.0	9.0	8.7	6.9	1.8	0.00	No. 1 Low " " " "
May 9-May 15	83.3	28.6	7.5	5.8	1.7	0.00	No. 2 High " " " "
May 22-May 26	21.4	14.2	7.7	5.2	2.4	0.00	No. 1 Low " " " "
June 10-June 16	15.1	7.5	7.8	5.2	2.6	0.00	No. 1 Low " " " "
Soluble organic phosphorus							
Mar. 10-Mar. 16	12.8	2.5	2.0	1.80	0.37	0.00	No. 1 Low " " " "
Apr. 12-Apr. 18	78.7	51.1	4.1	3.90	0.16	0.00	No. 2 High " " " "
Apr. 28-May 1	16.0	4.3	2.0	1.40	0.56	0.00	No. 1 Low " " " "
May 9-May 15	83.3	52.1	6.2	5.30	0.95	0.00	No. 2 High " " " "
May 22-May 26	21.4	3.7	2.2	1.70	0.52	0.00	No. 1 Low " " " "
June 10-June 16	15.1	4.1	1.6	0.98	0.64	0.00	No. 1 Low " " " "
Inorganic phosphorus							
Mar. 10-Mar. 16	12.8	2.63	14.2	2.8	11.3	0.10	No. 1 Low " " " "
Apr. 12-Apr. 18	78.7	2.60	56.6	44.1	8.6	3.90	No. 2 High " " " "
Apr. 28-May 1	16.0	2.60	13.1	4.9	7.9	0.37	No. 1 Low " " " "
May 9-May 15	83.3	2.60	57.2	45.6	6.7	4.90	No. 2 High " " " "
May 22-May 26	21.4	3.50	12.7	2.6	10.0	0.11	No. 1 Low " " " "
June 10-June 16	15.1	3.40	11.9	3.2	8.6	0.12	No. 1 Low " " " "

Weight of cow 1100 lbs., 3 months advanced in lactation period. Dates of last period corrected with approval of one of the authors.

DAILY PHOSPHORUS METABOLISM WITH MILCH COWS

EXPERIMENT II

Dates	Total P fed	Daily income and outgo					Rations
		Fed	Outgo	Feces	Milk	Urine	
Total phosphorus							
Dec. 27-Jan. 2		37	42.0	24.4	17.5	0.12	No. 1 Oat straw 10 lbs., washed bran 10 lbs., corn germ meal 6 lbs., rice meal 3 lbs.
Jan. 13-Jan. 19		18	30.2	11.6	18.5	0.09	No. 2 Oat straw 10 lbs., washed bran 10 lbs., wheat gluten 2 lbs., rice meal 7 lbs.
Jan. 27-Feb. 2		37	39.8	22.1	17.6	0.07	No. 1 High nucleo-phosphorus.
Feb. 10-Feb. 16		20	29.2	10.9	18.2	0.07	No. 2 Low " "
Nucleo-phosphorus							
Dec. 27-Jan. 2	37	21.5	11.4	8.0	3.4	0.00	No. 1 High " "
Jan. 13-Jan. 19	18	9.5	9.7	6.1	3.6	0.00	No. 2 Low " "
Jan. 27-Feb. 2	37	21.2	11.4	7.9	3.5	0.00	No. 1 High " "
Feb. 10-Feb. 16	20	11.4	10.5	6.8	3.7	0.00	No. 2 Low " "
Soluble organic phosphorus							
Dec. 27-Jan. 2	37	11.1	3.3	1.4	1.9	0 00	No. 1 High " "
Jan. 13-Jan. 19	18	4.1	3.2	1.4	1.8	0.00	No. 2 Low " "
Jan. 27 Feb. 2	37	11.2	3.2	1.5	1.7	0.00	No. 1 High " "
Feb. 10-Feb. 16	20	4.8	2.9	0.7	2.2	0.00	No. 2 Low " "
Inorganic phosphorus							
Dec. 27-Jan. 2	37	4.7	27.3	15.0	12.1	0.12	No. 1 High " "
Jan. 13-Jan. 19	18	4.7	17.3	4.1	13.1	0.09	No. 2 Low " "
Jan. 27-Feb. 2	37	4.7	25.3	12.7	12.5	0.07	No. 1 High " "
Feb. 10-Feb. 16	20	4.7	15.8	3.4	12.3	0.07	No. 2 Low " "

Weight of cow 966 lbs.

DAILY PHOSPHORUS METABOLISM WITH MILCH COWS

EXPERIMENT III

Dates	Total P fed	Daily income and outgo					Rations
		Fed	Outgo	Feces	Milk	Urine	
Total phosphorus							
Mar. 12-Mar. 18	77	77	68.4	43.5	14.7	10.17	No. 1 Oat straw 10 lbs., wheat bran 10 lbs., rice meal 7 lbs., wheat gluten 1½ lbs.
Mar. 30-Apr. 5	16	16	26.8	10.9	15.8	0.08	No. 2 Oat straw 10 lbs., washed bran 10 lbs., rice meal 7 lbs., wheat gluten 2 lbs.
Nucleo-phosphorus							
Mar. 12-Mar. 18	77	23.2	13.4	9.9	3.5	0.00	No. 1
Mar. 30-Apr. 5	16	9.6	9.4	6.1	3.3	0.00	No. 2
Soluble organic phosphorus							
Mar. 12-Mar. 18	77	50.2	1.58	0.53	1.05	0.00	No. 1
Mar. 30-Apr. 5	16	2.6	1.86	0.69	1.17	0.00	No. 2
Inorganic phosphorus							
Mar. 12-Mar. 18	77	4.0	53.4	33.1	10.2	10.10	No. 1
Mar. 30-Apr. 5	16	4.2	15.5	4.2	11.2	0.08	No. 2

Weight of cow 966 lbs.

Mendel and Underhill (1906)) conducted a series of balance experiments with a female dog on a diet of meat, cracker meal and lard. In some periods sodium phytate was administered subcutaneously, and in others the salt was given by the mouth. The basal ration was composed of hashed meat 72 gm., cracker meal 76 gm. and lard 14 gm.; the whole containing 3.84 gm. nitrogen, 1.01 gm. P_2O_5 and 520 calories. The numerical data are on page 311.

A part of the authors' conclusions are as follows:

"Comparatively large doses of phospho-organic acid, used as the sodium salt, can be introduced into animals either *per os,* subcutaneously, intraperitoneally, or intravenously, without unfavorable effects. The free acid is more toxic.

"No marked or immediate characteristic effects of the sodium salt upon general health or nitrogenous metabolism have been observed. The compound is readily absorbed and speedily transformed within the organism. Its phosphorus reappears in the excreta as inorganic phosphates. No constant relation between the metabolism of nitrogen and of phosphorus was observed. In these details our experience with the dog corresponds with the observations of Jordan, Hart and Patten after feeding phytin to cattle. Our results differ in showing that in both the dog and the rabbit the excess of phosphorus was almost entirely eliminated through the kidneys rather than in the feces. This may have an important bearing on the possibility of producing laxative effects with phytin.

"In our experimental animals purgative action could not be constantly provoked. Very large doses were frequently effective. No permanent generalizations can be drawn from the observations made on this point."

The authors also call attention to the fact that the effects, with their sodium salt, may differ from the natural phytin, because of the character of the bases present.

Horner (1907) conducted balance experiments with a dog and a rabbit which apparently showed that phytin may be absorbed and retained, though the results are not considered by Horner as quite conclusive.

McCollum and Hart (1908) demonstrated that calf's blood and liver have, but muscle and kidney have not, the property of cleaving phytate with the production of inorganic phosphate. They cite the conclusion of Scofone that the enzymes of the digestive tract do not alter phytin.

Hart, McCollum and Humphrey (1909) conducted a balance experiment covering about three and one-half months, with one cow,

PHYTIN METABOLISM EXPERIMENTS WITH A DOG—Grams

Date	Body weight	Urine		Feces		Nutritive balance						
						Nitrogen			P_2O_5			
	Kilos	Total N	P_2O_5	Total N	P_2O_5	Intake	Output	Balance	Intake	Output	Balance	
Nov. 12-14.....	6.5-6.5	9.42	1.24	0.77	0.19	11.5	10.2	+1.3	3.03	1.42	+1.61	Control period.
Nov. 15-17.....	6.5-6.6	8.82	1.68	0.77	0.24	11.5	9.6	+1.9	3.64	1.93	+1.71	Fed Na salt; 620 mg. P_2O_5.
Nov. 18-21.....	6.7-6.8	12.09	2.71	1.12	0.34	15.4	13.2	+2.2	5.90	3.05	+2.85	Fed Na salt; 1.86 gm. P_2O_5. Diarrhoeal stool.
Nov. 22-24.....	6.8-6.8	9.00	2.77	0.79	0.26	11.5	9.8	+1.7	4.89	3.03	+1.86	Fed Na salt; 1.86 gm. P_2O_5 in three doses.
Nov. 25-27.....	6.8-6.8	9.36	1.42	0.93	0.27	11.5	10.3	+1.2	3.03	1.69	+1.34	Control period.
Nov. 28-30.....	6.8-6.8	10.70	3.58	0.80	0 23	11.5	11.5	0	4.89	3.81	+1.08	Subcutaneous injection of Na salt; 1.86 gm. P_2O_5.
Dec. 1-3.....	6.8-6.8	9.90	1.47	0.93	0.18	11.5	10.8	+0.7	3.03	1.65	+1.38	Control period.
Dec. 4-6.....	6.8-6.8	10.62	2.43	0.84	0.25	11.5	11.5	0	3.96	2.68	+1.28	Subcutaneous injection of Na salt; 0.93 gm. P_2O_5.
Dec. 7-9.....	7.0-7.0	9.42	1.37	0.97	0.27	11.5	10.4	+1.1	3.03	1.64	+1.39	Control period.
Dec. 10-12.....	7.0-7.0	11.16	2.38	1.10	0.34	11.5	12.3	−0.8	3.62	2.72	+0.90	Subcutaneous injection HNa_2PO_4; 0.59 gm. P_2O_5.
Dec. 13-15.....	7.0-7.0	9.50	1.45	0.93	0.07	11.5	10.4	+1.1	3.03	1.53	+1.50	Control period.
Dec. 16-18.....	7.0-7.0	10.65	1.98	0.90	0.31	11.5	11.5	0	3.36	2.29	+1.07	Subcutaneous injection HNa_2PO_4; 0.33 gm. P_2O_5.
Dec. 19-21.....	7.0-7.0	10.68	2.17	0.98	0.12	11.5	11.7	−0.2	3.96	2.29	+1.67	Subcutaneous injection of Na salt; 0.93 gm. P_2O_5.

in a study of phytin metabolism. The phytin was as present in wheat bran, and as prepared from the same as a crude potassium salt. Whole bran was compared with washed bran, and with washed bran plus potassium phytate. The washing process removes, of course, a great variety of compounds other than the one of especial interest.

These authors reached the conclusion that the phytin of wheat bran does not have a specific effect on the production of milk, or on the production of fat in the milk, and that previous results, apparently showing such effects, have been due to the individuality of the subjects. Phytin was found to be diuretic because of its potassium content, and also laxative because of the elimination of phosphorus and accompanying bases by way of the feces.

Cook (1909) conducted a metabolism and tissue analysis experiment with six rabbits, in the comparison of phytin with sodium phosphates, when taken in excess of the maintenance requirement. Two rabbits were fed on corn, oats, and vegetables as controls; the remaining four received a ration of carrots, wheat gluten, starch, sugar, olive oil and salt mixture, two receiving phytin in addition, and the other two inorganic phosphorus in the shape of sodium dihydrogen phosphate and disodium hydrogen phosphate. The phytin was prepared from wheat bran. The condensed nitrogen and phosphorus balance data are as follows:

AVERAGE DAILY NITROGEN AND PHOSPHORUS (P_2O_5) BALANCES WITH RABBITS COMPARING PHYTIN AND SODIUM PHOSPHATES—Grams

Dates	Rabbit No.	Weight, average	Nitrogen		Phosphorus P_2O_5)		Form of phosphorus
			Intake	Balance	Intake	Balance	
Nov. 17-Feb. 15....	1	1618	1.154	+0.23	0.381	+0.14	Phytin
	2	1645	1.353	+0.32	0.415	+0.14	Phytin
	3	1585	1.520	+0.38	0.501	+0.18	Phosphate
	4	1981	1.396	+0.33	0.459	+0.18	Phosphate
Feb. 17-Mar. 15....	1	1550	1.479	+0.26	0.456	+0.166	Phytin
	3	1796	1.747	+0.40	0.541	+0.166	Phosphate
	4	1994	1.485	+0.18	0.498	+0.156	Phosphate

These data do not show unmistakable differences in the value of these compounds under the conditions of these experiments. It is worthy of note that the calcium and magnesium balances were positive. A part of the inconclusive character of the results must be due to the fact that there was loss of live weight in 5 out of the 7 periods.

The tissue analyses revealed more decided differences, though their significance is as yet unexplained. The autopsy revealed ab-

normal conditions in the livers, kidneys and lungs of the rabbits which received the phosphorus compounds, the livers all being pale in color, and enlarged. The livers of the rabbits which had received phytin showed marked fatty degeneration, as also did one of those receiving inorganic phosphates, though in a less pronounced way. The kidneys of the inorganic phosphate rabbits showed parenchymatous degeneration. Below are analytical data from several tissues of these rabbits.

CHEMICAL ANALYSES OF BODIES OF RABBITS AS AFFECTED BY PHYTIN AND INORGANIC PHOSPHATE—Dry Basis—Percent

Tissue	Nitrogen	Ash	Calcium	Magnesium	Ether extract	Phosphoric acid			
						Total	Ether-alcohol-soluble	Ether-alcohol-soluble in terms of total	
Bones....	4.53	55.56	8.86	0.22	11.33	23.96	0.055	0.23	
Livers...	7.64	3.78	0.00	0.00	44.95	1.98	0.680	34.34	
Blood....	14.72	5.64	Trace	0.00	Trace	0.75	0.008	1.07	Mean of rabbits 1 and 2 fed organic phosphorus.
Brains...	6.12	7.00	0.31	0.09	43.23	3.96	2.350	59.34	
Nerves...	5.52	6.54	0.21	0.11	46.96	3.72	2.390	64.26	
Teeth....	....	74.65	24.73	1.35	.....	35.31	.....	.....	
Bones....	4.68	55.92	7.74	0.15	9.39	26.33	0.061	0.23	
Livers...	9.41	4.73	0.00	0.00	34.48	2.56	0.854	33.36	
Blood....	14.42	4.72	Trace	0 00	Trace	0.69	0.008	1.16	Mean of rabbits 3 and 4 fed inorganic phosphorus.
Brains...	6.52	7.17	0.27	0.06	43.89	4.07	1.160	28.51	
Nerves...	3.72	5.53	0.28	0.06	47.34	4.28	1.470	34.35	
Teeth....	....	76.10	24.65	1.22	.....	34.70	.....	.....	
Bones....	4.32	57.47	10.17	0.23	5.12	25.93	0.069	0.27	
Livers...	11.90	5.67	0.00	0.00	14.47	2.85	1.090	38.24	
Blood....	14.42	4.55	0.44	0.19	Trace	0.58	0.037	6.33	Mean of rabbits 5 and 6 normally fed.
Brains...	6.85	7.82	0.51	0.08	38.50	4.16	1.750	42.07	
Nerves...	4.39	5.97	0.44	0.12	44.34	3.90	2.310	59.23	
Teeth....	....	75.17	28.35	1.15	.....	35.63	.....	.....	

Among the more prominent results here set forth are: (1) the low calcium content of the tissues, (2) the increase above normal of the alcohol-ether soluble phosphorus of the brain of the rabbits which received phytin, and (3) the decrease below normal of the alcohol-ether soluble phosphorus of the brain and nerves of the rabbits which received inorganic phosphates.

Tyshnjenko (1909) found, in balance experiments with 5 laboratory assistants on a diet of bread, meat, milk and butter, that the addition of sodium glycerophosphate caused a loss of phosphorus from the body, while phytin led to retention. We have seen only Maly's abstract of this article of 117 pages.

Starkenstein (1910) states that the organs of infants contain larger amounts of inosite than those of adults, and that it originates in the inosite-phosphoric acid of the food, which adults are able, in larger part than infants, to decompose, the remainder passing off

unchanged in the urine. Starkenstein, therefore, regards inosite as of no physiological importance in the animal body, but as a waste product of phosphoric acid metabolism; and he considers inosite-phosphoric acid as of importance only as a source of phosphorus, and also of value in certain pathological conditions of the osseous system. We shall stand in a fair way to clear up these problems when we have discovered a satisfactory method for the estimation of inosite-phosphoric acid.

Rogoziński (1910) studied phosphorus metabolism in an adult dog in 7 continuous 5-day experiments, without intervals between collection periods. Phytin, lecithin and sodium phosphate were added, in different periods, to a diet of meat, rice and lard. Rogoziński found no pronounced influence of these compounds on the nitrogen excretion in the urine, when they were added to a ration sufficient to maintain the animal.

The phosphorus of the sodium phosphate appeared quantitatively in the urine. The total lecithin fed to the dog was split, and the phosphorus excreted in the urine as inorganic phosphate; the phosphorus of phytin passed into the urine to the extent of about 30 percent of the total, the remainder being excreted in the feces, where it could be determined as such; the nitrogen and phosphorus balances were found to a high degree independent of each other.

In a 15-day experiment on himself Rogoziński added 2 gm. of phytin to a mixed diet (which was not analyzed) on the 6th to 10th days. The phytin was completely split in the digestive tract; a small part of the phytin phosphorus was retained, and the rest was excreted as inorganic phosphorus in the feces; the feces contained an abundance of lecithin-like compounds; no inosite was found in the urine after feeding phytin; the bacteria of human feces can split off inorganic phosphoric acid from phytin.

Donath (1911) reports phytin as a powerful stimulant to the appetite, and states that, in dogs having Pawlow fistulae, it increases the flow of gastric juice.

Sodium phytate in large quantities was found toxic to rabbits by A. R. Rose (1911). It appears that 1.7 gm. per kilogram of body weight is fatal. Rose (1912a) has conducted an extensive study on the metabolism of phytin with a milch cow. Organic as well as inorganic phosphorus of the food was eliminated very largely in the form of inorganic phosphorus in the feces, the amount of phosphorus in the urine being very small. The addition of calcium phytate increased the potassium, both in the urine and feces, and changed the path of elimination of part of the magnesium from the kidney to the intestine. The calcium added as calcium phytate was almost

entirely eliminated by the intestine immediately after administration. The calcium of the urine increased with decreasing phosphorus in the rations, and decreased when calcium phytate was added. The volume of the milk fluctuated inversely, and the total amount of fat in the milk directly, as the amount of phytin phosphorus in the rations. The increase of milk flow on removal of the phytin was not a mere dilution. Except for the change (increase) in the amount of fat, the composition of the milk was not materially altered.

These results sustain the earlier work of Jordan, Hart and Patten, but since the cow used by Rose was one of the same that were used in the work of Jordan, Hart and Patten, the factor of individuality was not excluded.

G. di Gregorio (1912) concluded that the administration of 1-2 gm. daily of phytin can check a pathological phosphaturia, and under normal conditions can diminish loss of phosphorus.

Santonocetto (1912) studied nitrogen metabolism as influenced by the administration of phytin. He concluded that under the influence of phytin the breaking-down of the cells is retarded, and the absorption of food nitrogen is promoted, the fecal nitrogen being reduced 30-75 percent, and the urine nitrogen 7.12 percent.

Venturi and Masella (1913) studied the influence of phytin ingestion on the balance of nitrogen, and on the qualitative distribution of the nitrogenous metabolites. The experimental subject was one of the authors. After a preliminary period of 4 days phytin was administered in the amount of 1.5 gm. daily for 5 days; then followed an after-period of 2 days, and a second phytin period of 5 days, during which 2.5 gm. of the compound was fed daily. The daily data show, in the phytin periods as compared with the fore- and after-periods, a marked decrease of urinary nitrogen, especially in the form of urea, creatinin, hippuric acid and xanthin bases, the uric acid and ammonia remaining without great change. The feces nitrogen was decreased, the nitrogen retention being prominently increased. The authors note the agreement of their results with those of Santonocetto. See also Forbes and associates (1914), Nutr. Val. Org. and Inorg. P.

CLINICAL EXPERIMENTS WITH PHYTIN

Sécheret (1904) made a historical and critical study of phytin therapy, with some observations on animals after the introduction of phytin, and also of 61 human patients under treatment with phytin. Most of the animals receiving phytin, otherwise than by the mouth, died soon. Hypodermic injections were, therefore, not

recommended. Dosage was discussed, and phytin recommended in a great number of pathological states, especially as a general tonic, and to increase the blood corpuscles, in constitutional debility, from whatever cause. Phytin is said to possess a very active pharmacodynamic action, exciting the internal nutrition of the tissues and cells, and increasing the nitrogen elimination.

Bardet (1905) has given study to the condition of general "demineralization," which may be due to any such illness of long standing as results in a disturbance of the normal balance between assimilation and losses. Of 17 cases examined 4 are reported; one a woman 23 years old, in a low state because of a long siege of typhoid fever; another was a wet-nurse, aged 28, who was in a debilitated state; a third was a boy 16 years old who had become highly neurasthenic through overstudy; and a fourth was a rapidly growing boy of 14 years, who was in a much disturbed state. Adrian's extract of cereals (containing 4 percent P_2O_5, and considerable potassium, magnesium and some manganese, all in organic combination, largely as a phytin) was administered with sodium methyl arsenate. Fifteen to twenty-five grams of the extract were given in solution each day for 30 or 40 days, which treatment brought about almost complete restoration to normal condition. Since this cereal extract contained in assimilable form nutrients of which the body stood in need, it was probably of some value, though the use of arsenic adds a factor to the problem which makes impossible a positive interpretation of the results.

Novi (1908) submitted data apparently showing that the administration of phytin, 1-1.5 gm. per day, decreased the urinary phosphorus in antirabes treatment from 69.11 to 46.07 percent of the intake. Feces figures were not submitted.

Novi (1909) reported that in consequence of the injection of 1-percent water solution of phytin into the dorsal lymph sack of the frog the muscle power was 2-4 times higher than normal. Calcium chloride produced no such effect, but a mixture of sodium, magnesium and calcium chlorides produced the same effect as the phytin, as also did magnesium chloride alone. Sodium glycerophosphate produced no effect, but calcium glycerophosphate doubled the muscular power.

Favorable results from the use of phytin, by ingestion, in cases of gastric ulcer are reported by Wolpe (1911).

Other clinical reports from the use of phytin in human medical practice are those of Loewenheim (1904), Gilbert and Lippmann

(1904), Fürst (1904), Gianasso and Ovazza (1905), Winterberg (1905), Dambre (1905), Wechsler (1905), Maëstro (1905a), and Weissmann (1908). The results of these studies have been almost uniformly favorable, as shown by improved state of nutrition generally, increased appetite, improved blood conditions, etc. Emphasis is placed on the fact of the very high phosphorus content of this compound, making it a superior vehicle for the administration of phosphorus in an organic form.

Summary. Conservatism in the acceptance of results in the clinical study of phytin is especially to be recommended because of the abundance of phytin and related compounds in some of our common foods, which produce no marked specific symptoms. On the other hand, we are obliged also to admit the possibility that this compound as administered in an uncombined state may have a different effect and method of usefulness from the same as normally combined in foodstuffs. There is not the same ground for this latter hypothesis, however, that there is in the case of lecithin, since phytin even though absorbed as such, unsplit, must be broken up before it can be of use for constructive purposes, phytin not being a constituent of the animal body.

A measure of uncertainty must exist in regard to results in this field until an understanding of the chemistry of phytin and related compounds has been attained. It seems quite probable that the name phytin has been associated with a variety of compounds. There is no question, however, as to the absorbability of phytin, nor of its usefulness in animal metabolism.

Phytin is readily soluble in the hydrochloric acid of the gastric juice and is mostly absorbed without decomposition by the digestive enzymes. It is decomposed, however, before utilizaton by the tissues, and to such extent as it is not retained, its phosphorus is eliminated in the urine and feces. In cattle and in human beings phytin phosphorus is eliminated as inorganic phosphates, following the usual course as determined by the nature of the diet and by the inorganic bases present. In dogs, however, a considerable part of the phytin phosphorus seems to be eliminated in the feces, where it is found present as phytin.

The power to split phytin has been found to reside in the blood and liver, but not in the muscle and kidney of the calf. It may also be decomposed by intestinal bacteria.

The contribution of phytin to the laxative and diuretic effects of rations is through the inorganic bases contained. There has not yet been established a definite relation between phytin ingestion and nitrogen metabolism.

We are not yet able to say whether or not phytin has specific effects in animal nutrition, but there is certainly nothing strikingly characteristic about the method of its use. Apparently, at least its chief superiorities as a phosphorus-carrying nutrient lie in its ready solubility and in its high phosphorus content.

THE NUTRITIVE VALUES OF ORGANIC AND INORGANIC PHOSPHORUS

METABOLISM EXPERIMENTS WITH MEN AND ANIMALS

Considering the phosphorus of the animal body as a whole the most obvious distinction among the various groups of its compounds is that certain of these are organically combined, as a part of the living tissue, being fundamentally involved in all vital activities, while others are simple salts of the mineral bases either deposited in supporting structures or dissolved in the body fluids.

In both cases the phosphorus itself, so far as known, is present in the same completely oxidized form as phosphoric acid, differing only in its chemical relationships. This discussion is a consideration of the evidence as to the nutritive limitations imposed by these differences in relationship of phosphoric acid. We wish to know whether organic and inorganic phosphorus compounds can serve, equally well, all the requirements of the body for phosphorus under all conditions of life.

Let us consider first the eggs of birds, for the egg assuredly contains all of the nutrients required by the fully formed animal. Examining the phosphorus of eggs we find a wealth of organic compounds but, at the most, mere traces of inorganic phosphates. It is thus obvious that organic phosphorus compounds can serve all of the needs of the body for this element. But our interest is in foodstuffs; let us consider the first natural food of young mammals, the mother's milk. Are the comparative amounts of organic and inorganic phosphorus related to the food requirements of the young animal, or do they simply represent their relative availability for milk production in the maternal organism? However this may be, if there is not an adaptation of the character of the food to the requirements of the young, then there must be an adaptation of the method of development of the young to the possibilities of the food, in either case a harmony of objects to be attained and means for their attainment.

In this light we would naturally assume that both organic and inorganic phosphorus compounds are of benefit to the animal; for

both classes are represented in milk by several individuals each, and in the whole literature of the subject there is scarcely a dissenting voice raised against this idea. Both organic and inorganic phosphorus are absorbed and retained.

But now we come to the parting of the ways. If organic phosphorus can serve all of the requirements of the body for phosphorus, and if inorganic phosphorus can be absorbed and retained, are organic and inorganic phosphorus equally useful for all of the purposes for which the body needs phosphorus? Our economic reason for desiring an answer to this question lies in the relative accessibility of organic and inorganic phosphorus for use as food. If rock phosphate and old bones can furnish us phosphorus in the forms most advantageous for the growth of animals, we are wasting much money on milk, eggs and beef; for there are much cheaper sources than these, of protein, fat and carbohydrates.

In this consideration let us bear in mind that our interest as agricultural scientists is not so much in bare physiological minima as in maximum practical optima, for the whole range of success and profit in animal production lies close to the latter.

It would seem that so simple a problem ought readily to be solved, but when we approach the subject by direct experiment we find the course beset with hazards, and there never has been unanimity of opinion as to the facts. Among those circumstances which have contributed to this difference in opinion are:

(1) An inclination to ascribe to all animals under all conditions of life all capacities of synthesis possessed by any animal under any condition, natural or experimental, no matter how great the stress of attending circumstance.

(2) Drawing conclusions from very short balance experiments, without due regard to states and habits of nutrition as determined by previous feeding.

(3) A failure to distinguish between physiological minima and practical optima.

(4) Drawing conclusions from mere gain in weight, without actual estimation of the compounds of interest or measurements of functional efficiency in the experimental animals and in carefully selected controls, the error in so doing being that it implies the maintenance of constancy of composition and function, the variability of which, as affected by feeding, is usually underestimated.

(5) Drawing conclusions from analyses of parts of animals, a complete chemical accounting being desirable.

(6) Failure fairly to meet the great difficulties of compounding rations which do not differ in essential ways other than in the point of interest, that is, in the *condition* in which the phosphorus is present.

(7) It is quite possible that useful enzymes associated with the organic phosphorus compounds have exerted a determining influence on the results.

(8) Unsatisfactory mineral salt accompaniments may have affected the usefulness of the phosphorus compounds in such ways as to result in unfair comparisons.

(9) The specific physiological action of isolated compounds of phosphorus, as used in nutrition investigations, undoubtedly differs from the effects of the same compounds in their natural relationships in foodstuffs.

We shall review, in brief, the evidence on the subject.

W. S. Hall (1896), from feeding experiments with mice, came to the conclusion that the salts organically combined with casein have a value greater than salts not so combined.

Steinitz (1898) conducted balance experiments on dogs to compare organic and inorganic phosphorus compounds as nutrients. Nutrose, a sodium-calcium-casein compound, vitellin, and myosin prepared from horse flesh were each added, in different periods, to a basal ration of bacon, rice starch and mineral salts; the casein preparation and the vitellin both containing organic phosphorus, and the myosin being at least practically free from organic phosphorus. Phosphorus was stored abundantly on the organic phosphorus rations, but the retention was almost nothing on the myosin ration, though in all cases, including the myosin ration, nitrogen was stored in considerable quantity. The salt mixture used with the organic phosphorus compounds contained chlorides and citrates only, while the salts used with the myosin were calcium, magnesium and potassium phosphates, sodium chloride and ferric citrate. The experimental periods were 5-9 days each, following 8-day fasting periods.

Rohmann (1898) found, in balance experiments on a dog, with a diet of lard, rice starch, salt and either a phosphorus-containing protein, or a phosphorus-free protein and a phosphate, that both nitrogen and phosphorus retention were favored by the phosphorus-containing protein much more than by the phosphorus-free protein and phosphate. With nutrose and vitellin the nitrogen retention was 31.0 and 42.2 percent, respectively, of the intake; while with myosin and edestin the retention was but 0.10 and 0.11 percent of the intake. Likewise with the nutrose and vitellin the phosphorus retention was 8.8 and 20.9 mg. per day, while with myosin and edestin the retention was 0.1 mg. per day in both cases.

Leipziger (1899) studied metabolism in a dog on a ration which was very low in organic phosphorus. The ration was composed of edestin, fat, starch, salt, beef extract and water. The dog was fasted for 6 and 10 days, respectively, in the fore-periods of two tests, and then fed for 6 days in each of the two main periods.

The phosphorus intake in the two experiments was 1.874 and 2.022 gm. per day, of which 0.016 and 0.022 gm. was organic. The dog retained 0.0078 and 0.095 gm. of phosphorus per day in these tests, the nitrogen and calcium balances also being positive. The subject of these experiments was the dog referred to as "Dog II" in Steinitz's experiments.

Leipziger considered that his data did not afford evidence as to the condition in which the phosphorus was retained, but thought that synthesis of phosphorus-containing protein from phosphorus-free protein and phosphates was improbable; also that the phosphorus retention was less than it would have been on a ration containing more phosphorized protein. The organic phosphorus content of this ration was sufficient to render impossible the solution of the problem of phosphorized protein synthesis except by negative results—which were not obtained.

Zadik (1899) conducted nitrogen and phosphorus balance experiments with dogs in the comparison of phosphorized proteins with phosphorus-free proteins and inorganic phosphates. The compounds of interest were casein, vitellin and edestin. The basal ration was composed of starch, bacon, sodium citrate or carbonate, and a salt mixture of phosphates, chlorides, magnesium citrate and sugar. The numerical data contain numerous inconsistencies, on account of which we do not transcribe them, but the errors seem not to be of a degree to modify at all the significance of the results. With casein or vitellin there was marked retention of phosphorus; with edestin and disodium phosphate there was always loss.

Zadik concluded that the animal organism does not have the power to build from phosphorus-free proteins and phosphates the organic phosphorus compounds necessary for the life of the cells. The organic phosphorus of casein and vitellin was, under his experimental conditions, at least, more useful than the inorganic phosphates; also, the phosphorus of vitellin was stored in larger proportion to the intake than was the phosphorus of casein.

Ehrlich (1900) conducted five balance experiments with dogs in a comparison of phosphorized proteins with phosphorus-free protein plus inorganic phosphates. The results tend to show that the phosphorized proteins, casein and vitellin, have a greater useful-

ness to the animal, in the sense of favoring phosphorus retention, than does the phosphorus-free edestin plus inorganic phosphates. The periods were 3-7 days in length. Certain unfavorable conditions render the results of doubtful value.

Kornauth (1900) compared synthetic "nucleins," prepared after the method of Liebermann, by the precipitation of egg albumin and blood serum albumin with metaphosphoric acid, with natural proteins in the form of meat, skin, aleuronate (a vegetable casein), casein and conglutin (from lupines). The results on maintenance of nitrogen equilibrium hardly warrant conclusions, but the evidence is quite satisfactory in showing that, for maintenance of phosphorus equilibrium, very much more phosphorus in the so-called synthetic nucleins is necessary than of phosphorus in the natural proteins.

Steinitz (1900) reports several attempts to rear young dogs on artificial food mixtures containing their protein as casein, edestin, milk, nucleoprotein from calf liver, and vitellin. Other foods used were rice starch, lard, bacon and inorganic salts. The experiments were mostly of short duration, on account of unfavorable termination. None were carried through to a satisfactory demonstration of the sufficiency of the diet.

Gottstein (1901) conducted a metabolism experiment with a dog in two five-day balance periods in which casein was opposed to edestin. The results were inconclusive.

Ehrström (1903a) conducted an experiment which bears on the relative value of organic and inorganic phosphorus. The condensed data are as below.

DAILY NITROGEN AND PHOSPHORUS BALANCES WITH A GROWN MAN RECEIVING ORGANIC AND INORGANIC PHOSPHORUS COMPOUNDS—Grams

Length of balance period	Diet	N Intake	N Balance	P Intake	P Balance
7 days	Freely chosen diet of ordinary foods	+17.37	−1.33	+2.476	+0.610
6 days	Proton-bread and milk	+17.86	+0.58	+2.090	+0.642
5 days	Ordinary white bread, milk and $CaHPO_4$	+12.55	−1.81	+2.271	+0.227

Less phosphorus was stored when a certain portion of the total was administered as dibasic calcium phosphate than when the same amount was taken as proton—a casein preparation; in these last two periods, then, we have opposed to each other a typical phosphoprotein and an inorganic phosphate, added in each case to a bread and milk ration. The author does not submit data showing that the phosphate ration contained bases, especially calcium, sufficient in

amount, relative to acid elements, to render conditions as favorable for phosphorus storage as in the proton ration. The periods also are very short for mineral metabolism work. The data seem to show the organic phosphorus the more useful.

Hirschler and Terray (1902, 1905) compared bone dust with eggs as sources of phosphorus for growing dogs. A portion of the data are below.

METABOLISM EXPERIMENTS ON DOGS WITH ORGANIC AND INORGANIC PHOSPHORUS COMPOUNDS

Daily Amounts—Grams

Period and days	Gain or loss in weight of dog Kg.	Intake			Phosphorus outgo		Daily balances			Diet
		N	P_2O_5	CaO	Urine	Feces	N	P_2O_5	CaO	
1	4.130									
4 days	+0.010	5.419	1.377	0.686	0.681	0.139	+0.912	+0.557	+0.344	400 c.c. milk; 23.56 gm. dried meat.
2										
4 days	−0.015	5.419	1.377	0.686	0.688	0.217	+0.567	+0.472	+0.350	400 c.c. milk; 23.56 gm. dried meat.
3										
4 days	−0.005	5.419	1.377	0.686	0.677	0.227	+0.444	+0.499	+0.266	400 c.c. milk; 23.56 gm. dried meat.
4										
2 days	+0.025	5.419	1.765	1.212	0.656	0.403	+0.784	+0.711	+0.575	Same as above + 1 gm. bone dust.
5										
2 days	−0.010	5.419	1.377	0.686	0.667	0.361	+0.514	+0.350	+0.087	400 c c. milk; 23.56 gm. dried meat.
1	3.600									
4 days	+0.013	4.781	1.097	0.524	0.575	0.114	+0.688	+0.408	+0.176	300 c.c. milk; 23.56 gm. dried meat.
2										
4 days	−0.005	4.778	1.184	0.541	0.638	0.180	+0.798	+0.366	+0.148	300 c.c. milk; 15.06 gm. dried meat; 53.5 gm. egg.
3										
4 days	−0.013	4.781	1.097	0.524	0.611	0.353	+0.295	+0.132	+0.177	300 c.c. milk; 23.56 gm. dried meat.
4										
2 days	+0.020	4.781	1.485	1.050	0.548	0.717	+0.115	+0.220	+0.001	300 c.c. milk; 23.56 gm. dried meat; 1 gm. bone dust.
5										
2 days	0.000	4.781	1.097	0.524	0.625	0.379	+0.160	+0.094	+0.288	300 c.c. milk; 23.56 gm. dried meat.

Age of dogs, 2½-3 months.

Since the intake was not maintained constant, there was not an entirely satisfactory basis for comparison of phosphorus in the different forms. With one dog the bone dust caused increased retention of nitrogen, calcium and phosphorus, with no increase in urinary phosphorus, but naturally a decided increase in feces phosphorus. With the other dog the bone dust caused diarrhoea, and the results are perhaps affected by this disorder. Because of the rapid decline in the rate of phosphorus storage during the experiment with the second dog, it is impossible to say just what was the effect of the egg on phosphorus storage.

Gilbert and Posternak (1905) compared organic and inorganic phosphorus compounds in balance experiments with human subjects. A part of the data are in the following table.

DAILY NITROGEN AND PHOSPHORUS BALANCES FROM A NORMAL HUMAN SUBJECT WITH ORGANIC AND INORGANIC PHOSPHORUS COMPOUNDS ADDED TO A NORMAL RATION

Periods of Five Days Each—Grams

Ration	Nitrogen				Phosphorus (P_2O_5)			
	Food	Urine	Feces	Balance	Food	Urine	Feces	Balance
1. 300 gm. meat; 450 gm. dried bread; 30 gm. butter; 100 gm. sugar; 1600 c.c. tea.	17.96	17.72	2.45	−2.21	2.43	1.972	0.675	−0.217
2. Same as above plus mono- and di-calcium phosphates, 0.24 and 0.52 gm. P_2O_5.	17.96	16.62	2.33	−0.99	3.19	2.044	1.337	−0.191
Fore-period, constant diet for 5 days.	17.96	15.85	2.40	−0.29	2.43	1.916	0.643	−0.129
Same as above plus 0.593 gm. P_2O_5 as calcium glycerophosphate.	17.96	16.96	2.11	−1.11	3.02	2.272	0.853	−0.102
Same as above without added phosphorus.	17.96	16.24	2.42	−0.70	2.43	1.932	0.683	−0.185
Same as above plus 1 gm. per day P_2O_5 as calcium phytate.	17.96	16.94	2.20	−1.18	3.43	2.100	1.209	+0.121

Age of subject, 3 years.

In this experiment the phosphates and the glycerophosphate were not well retained, though they did serve slightly to reduce the phosphorus loss. Calcium phytate, however, brought about decidedly improved phosphorus retention and a positive phosphorus balance. The amount of phosphorus taken in this form, however, was much greater than in the other cases, so that we do not have an entirely fair basis for comparison. In consideration of the character of the basal ration, which must have been very low in calcium, it would also be important to know the calcium contents of the phosphatic supplements.

Gouin and Andouard (1905-6), in calf-feeding experiments, used potassium phosphate, bone phosphate, sweetbreads, thymus and protylin as sources of phosphorus. The nature of the data did not give a basis for a close estimate of the values of these compounds. The authors make the statement, however, that they found the bone phosphates more "digestible" than vegetable phosphates. In this connection, we would mention the fact that we have no means of determining the *digestibility* of such compounds.

Tunnicliffe (1906) conducted balance experiments with two healthy children, aged, respectively, 2 years, and 2 years and 10 months, comparing organic and inorganic phosphorus compounds, and their effects on nitrogen metabolism. A part of the data are as follows:

AVERAGE DAILY NITROGEN AND PHOSPHORUS BALANCES WITH HEALTHY CHILDREN RECEIVING ORGANIC AND INORGANIC PHOSPHORUS WITH THE FOOD—Grams

Subject	Period	Duration of periods in days	N Food Urine Feces Balance	P Food Urine Feces Balance	Diet
Boy, 2 years old.	Fore-period	2	5.95 2.21 0.98 +2.75	0.69 0.13 0.18 +0.38	Mixed normal diet.
Boy, 2 years old.	Organic phosphorus period	6	8.80 3.93 0.78 +4.08	0.96 0 27 0 20 +0.49	Same plus 20 gm. sanatogen.
Boy, 2 years old.....	Inorganic phosphorus period	3	5.76 3.39 0.88 +1.48		Same as first plus 1 gm. $Ca_3(PO_4)_2$.
Girl, 2 yrs. 10 mos. old	Fore-period	3	6.53 3.22 0.75 +2.56	0.73 0.31 0.15 +0.27	Mixed normal diet.
Girl, 2 yrs. 10 mos. old	Organic phosphorus period	6	9.14 4.70 0.72 +3.72	0.99 0.43 0.12 +0.44	Same plus 20 gm. sanatogen.
Girl, 2 yrs. 10 mos. old	Inorganic phosphorus period	3	5.80 2.62 0.76 +2.42	0.87 0.28 0.24 +0.35	Same as first plus 1 gm. $Ca_3(PO_4)_2$.

From these data Tunnicliffe concluded (1) that in the healthy child the addition of an organic phosphorus compound to the diet is followed by an increase in the amount of phosphorus assimilated by and retained in the body; (2) that the addition of an organic phosphorus compound to the diet of children increases the amount of nitrogen assimilated; (3) that the addition of $Ca_3(PO_4)_2$ to the food did not increase the amount of phosphorus assimilated or retained by the child, nor did this compound exert any favorable influence upon the assimilation of the nitrogen of the food; and (4) that the phosphorus contained in the sodium glycerophosphate of casein (sanatogen) is practically entirely assimilated by the body.

We would suggest that the periods are too short to give results of great value, and that, since the intake of nitrogen and phosphorus was greater in the organic phosphorus period than in the inorganic phosphorus period, these data do not furnish a fair basis for a comparison of the nutritive values of these compounds. At the same time it seems probable that the phosphorus of sanatogen *is* more useful than the same amount of phosphorus in $Ca_3(PO_4)_2$.

LeClerc and Cook (1906) conducted a series of nitrogen and phosphorus balance experiments with three rabbits and a dog, comparing phytin and inorganic phosphates, in twenty-six five-day periods. The phytin was prepared from wheat bran. This compound and a mixture of disodium hydrogen phosphate and dihydrogen sodium phosphate were added to normal and to phosphorus-poor rations.

From the considerable weight of the subjects it would appear that, if not mature, they were at least beyond the period of most active growth. During these experiments the live weights were practically constant; in half of the periods there was loss of weight, and in none of them was there marked gain in weight. These conditions, together with the brevity of the periods, were unfavorable to the demonstration of such differences in value as exist between these nutrients.

The authors state that the nitrogen retention was generally lowered by the addition of inorganic phosphates, when fed with a normal food; and that the organic phosphorus compound from wheat bran is more favorable to nitrogen and phosphorus retention than is inorganic phosphorus. See also Cook (1909), p. 312.

Egbert Koch (1906) investigated the question of synthesis of phosphorus compounds from edestin and inorganic salts by the human being, by means of a feeding experiment on a man. The results are shown in the following table. The subject was in a normal state of nutrition throughout the investigation.

AVERAGE DAILY NITROGEN, CALCIUM AND PHOSPHORUS METABOLISM OF A MAN ON RATIONS DIFFERING IN ORGANIC PHOSPHORUS CONTENT

Periods of Four Days Each—Grams

Rations	N Intake Urine Feces Balance	P_2O_5 Intake Urine Feces Balance	CaO Intake Urine Feces Balance	Weight Initial Final Difference Diff. per day Kg.
100 gm. oatmeal; 1500 c.c. milk; 6 gm. NaCl; 20 gm. cane sugar; 100 gm. butter; 500 c.c. tea; 300 c.c. wine; 150 gm. egg white.	13.46 10.31 1.10 +2.05	4.43 2.20 1.90 +0.34	2.991 0.137 2.500 +0.354	63.9 63.0 −0.9 −0.22
100 gm. oatmeal; 48.5 gm. edestin; 6 gm. NaCl; 70 gm. cane sugar; 180 gm. butter; 500 c.c. tea; 300 c.c. wine; 150 gm. egg white; 13.36 gm. Na_2HPO_4; 4.12 gm. $CaCO_3$; 1.5 gm. $CaHPO_4$.	12.97 10.10 0.97 +1.65	4.44 2.98 1.42 +0.04	2.997 1.420 3.038 −0.183	63.0 63.7 +0.7 +0.18

Calculated from author's data.

In the first ration the phosphorus was present to a considerable extent as phosphoprotein, that is, as casein. In the second ration the phosphorus was present principally as inorganic phosphates.

The intake of nitrogen, phosphorus and calcium was maintained practically constant, though the nitrogen intake in the second period was a little less than in the first.

In the inorganic phosphorus period the nitrogen storage was less, as also was the phosphorus storage, while the calcium balance changed from +0.354 gm. to —0.183 gm. From these data the author concluded that "the view that the human organism cannot effect a synthesis from phosphorus-free protein and inorganic phosphorus salts receives further support from these experiments."

Hart, McCollum and Fuller (1909) studied the role of inorganic phosphorus in the nutrition of swine by feeding, slaughter and balance experiments. The daily rations in their first experiment were as follows:

DAILY RATION AND AVERAGE GAIN IN WEIGHT

	Lot 1 Pounds	Lot 2 Pounds	Lot 3 Pounds	Lot 4 Pounds	Lot 5 Pounds
Ground rice	1.24	1.20	1.22	1.26	Ground corn 0.67
Washed bran	0.65	0.63	0.64		
Wheat gluten	0.26	0.25	0.26	0.27	Ground oats 0.67
Sugar-salt mixture (200 gm. sugar; 100 gm. each $NaCl$, $MgCl_2$, K_2SO_4)	0.048	0.046	0.047		Wheat middlings 0.67
Precipitated calcium phosphate ($Ca_3(PO_4)_2$ + $CaHPO_4$)		0.077	0.038		Oil meal 0.22
Whole bran				0.67	
	Grams	Grams	Grams	Grams	Grams
Total phosphorus	1.12	6.57	3.84	5.40	5.45
	Pounds	Pounds	Pounds	Pounds	Pounds
Average gain in weight	28.33	52.6	52.6	59.0	61.5

There were, all told, 16 pigs in this experiment. The experiment covered 95 days, after which one animal from each lot was killed, and some parts were analyzed for dry matter, calcium and phosphorus. The calcium and phosphorus data are as follows:

COMPOSITION OF PARTS OF PIGS—Air-Dry Basis—Percents

	Bone ash		Blood		Leg muscle		Liver		Brain	
	P	Ca	P	Ca	P	Ca	P	Ca	P	Ca
Basal, lot 1	18.48	37.16	0.24	0.035	0.93	0.030	1.43	0.020	1.49	0.08
Inorganic, lot 2	18.26	36.91	0.31	0 031	0.81	0.029	1.34	0.030	1.57	0.10
Whole bran, lot 4	18 00	37.12	0.33	0.038	0.77	0.025	1.35	0.066	1.54	0.09
Normal, lot 5	18.20	37.23	0.28	0.026	0.78	0.041	1.27	0.030	1.43	0.09

The skeleton of one animal from each lot, except the third, was dissected out and subjected to study as indicated by the following data:

DATA ON SKELETON OF ONE ANIMAL FROM EACH LOT OF EXPERIMENT I (EXCEPT LOT 3)

	Basal	Phosphate	Whole bran	Standard
Weight of skeleton, gm	1193	2371	1288	1609
Weight of animal, lbs.	84	123	102	138
Breaking strength of thigh bone, lbs. per sq. mm.	0.63	1.80	1.84	1.69
Diam. thigh bone at centre, mm	18.00	23.90	18.50	22.00
Sp. gr. of bones	0.977	1.157	1.100	1.192
Ash (thigh bone)	31 percent	55 percent	53 percent	46 percent

Experiment II was similar to the above, except that near the end of the program one animal from each of five lots was put into a metabolism crate, and subjected to a balance experiment of 5-12 days' length. The whole program covered 123 days.

In this experiment the rations used were as indicated below:

Lot 1—Low phosphorus basal ration.
" 2— " " " " +precipitated calcium phosphate
" 3— " " " " +bone ash
" 4— " " " " +floats (rock phosphate)
" 5—Basal ration with whole bran substituted for washed bran.
" 6—Normal foods.

The summarized balance data are as follows:

AVERAGE DAILY PHOSPHORUS BALANCES

	Aver. gain in weight of lot	Total phosphorus intake	Total phosphorus in urine	Total phosphorus in feces	Inorganic phosphorus in feces	Phosphorus retention
	Pounds	Grams	Grams	Grams	Grams	Grams
Basal	32	1.08	0.02	0.52	0.168	0.53
Precipitated phosphate	42	5.02	0.378	2.45	....	2.22
Bone ash	35	4.08	0.281	2.26	....	1.54
Floats	43	4.26	0.253	1.65	....	2.35
Whole bran	58	5.65	0.666	2.66	2.47	2.36

One animal from each lot in this experiment was killed, and below are data from the examination of the skeletons.

DATA ON THE SKELETON OF ONE ANIMAL FROM EACH LOT OF EXPERIMENT II (EXCEPT LOT 6)

	Basal	Precipitated phosphate	Bone ash	Floats	Whole bran
Weight of skeleton, gm	870	950	950	1495	850
Weight of animal at slaughter, lbs.	77	87	58	82	87
Breaking strength of thigh bone, lbs. per sq. mm.	0.87	1.70	1.77	1.65	1.86
Diam. thigh bone at centre, mm	16.0	16.0	15.5	20.00	17.00
Sp. gr. bone	0.984	1.15	1.12	1.19	1.14
Ash, percent (thigh bone)	33	46	53	57	54

The authors' conclusions are as follows:

"1. On the ration extremely low in phosphorus, pigs made as large gains up to 75 or 100 pounds when starting at weights of from 40 to 50 pounds as animals receiving an abundance of this element. After reaching this point loss of weight began, followed by collapse.

"2. When such low phosphorus rations as induced the above symptoms were supplemented with calcium phosphates, no untoward results appeared. Animals fed a low phosphorus ration, supplemented with inorganic phosphates, made as vigorous a development as others receiving their phosphorus supply wholly in organic form.

"3. Precipitated calcium phosphates, a mixture of di- and tri-calcium phosphates, gave no better results than did floats, a crude tri-calcium phosphate.

"4. Phytin as the supply of phosphorus gave no better results than the inorganic phosphates.

"5. A young animal of 40 pounds weight receiving inorganic phosphates, together with other salts as supplementary to a ration very low in mineral constituents, grew to be an animal of 280 pounds weight, bore a litter of fairly vigorous pigs, which on the same ration completed the cycle back to 80 pounds, while animals on the same ration less the inorganic phosphates collapsed in three months, with loss of weight accompanied by a loss of the use of their limbs.

"6. Determinations of calcium and phosphorus on the principal organs and tissues of the animals on the low phosphorus ration showed that they maintained the proportion of these elements constant and comparable to that of normally fed pigs.

"7. The percentage of ash in the skeleton of pigs on the depleted phosphorus ration was reduced to nearly one-half that of pigs receiving a normal ration, or a phosphorus-poor ration supplemented by an inorganic phosphate.

"8. The marked reduction in the quantity of ash of the bones of the animal receiving an insufficient supply of calcium phosphates, together with the ability of the animal to build up a skeleton very rich in calcium phosphate when an abundance of the latter is supplied in inorganic forms, strongly points to the possession of a synthetic power by the animal which enables it to convert inorganic forms of phosphorus into the organic forms demanded by its body.

"9. When animals were starving for phosphorus, they drew this element from the skeleton, but removed calcium and phosphorus in the proportions found in tri-calcium phosphate.

"10. The daily phosphorus supply for a 50-pound growing pig should be at least 3 gm. A supply of 4 or 5 gm. is probably a safer quantity.

"11. The data furnish no positive evidence of the synthesis of nucleo-proteids or other phosphorus-bearing complexes from inorganic phosphates in the animal body."

On these conclusions we would offer the following comments:

The basal ration used in these experiments was exceedingly low in calcium. To have furnished a wholly satisfactory basis for the comparison of the phosphorus compounds studied there should have been no question as to calcium deficiency limiting the usefulness of any of these preparations. In this light, the phosphorus of floats had the greatest advantage, since it was associated with an excess of calcium; the phosphorus of precipitated phosphate came next in order of relation of calcium to phosphorus, while the wheat bran phosphorus was associated with an exceedingly small proportion of calcium.

The authors' statement that the calcium and phosphorus content of the principal organs of the body was maintained constant is not sustained by their analytical data. True, there is a marked tendency toward the maintenance of constancy of composition, but, at the same time, there are, in the case of each of the five important parts analyzed, variations in the content of calcium and phosphorus, which, reckoned on the basis of the total amount of the constituent present, constitute marked deviations from the normal.

The authors' conclusion No. 8, citing the utilization of inorganic calcium phosphate in the building up of the skeleton as an evidence of "the possession of a synthetic power by the animal which enables it to convert inorganic forms of phosphorus into the organic forms demanded by its body," seems not to be warranted. Conclusion No. 11, which claims "no positive evidence of synthesis of nucleo-proteids or other phosphorus-bearing complexes from inorganic phosphates in the animal body," is more to the point.

These experiments seem not well planned to bring out differences in usefulness of organic and inorganic phosphorus. They do make emphatic one point, however; that the amount of organic phosphorus absolutely necessary to the life of the pig is, at the most, not a large part of the total phosphorus requirement.

Holsti (1910) attempted to settle the question of organic phosphorus synthesis by balance experiments on himself; but, as the rations differed in total phosphorus content by as much as the amounts added to some of them as inorganic phosphorus, there was

in reality no basis whatever, for judgment as to the matter of synthesis of organic phosphorus compounds. This much was demonstrated, however, that if the total phosphorus of the ration is adequate, a very small intake of organic phosphorus (about a third of a gram sufficed in one case) will permit of phosphorus retention, even coincident with nitrogen loss. Holsti's experimental periods, 3-6 days in length, were too short really to settle anything.

Under the title "Nuclein Synthesis in the Animal Body," McCollum (1909) published results of feeding experiments with rats on a basal ration composed of phosphorus-free foods, to which were added phosphorus-containing substances to be compared. Among the foods used were edestin, zein, corn starch, wheat starch, butter fat, bacon fat, milk sugar, glucose, cane sugar, and cholesterin. Many flavoring extracts were used in an effort to make the food palatable. Milk ash, calcium phosphate, sodium chloride and ferric chloride were also used in the basal ration, and casein, and hydrolyzed beef and liver were added to this ration in some periods.

McCollum concludes that, other things being satisfactory, all the phosphorus needed by an animal for skeleton, nuclein, or phosphatid formation, can be drawn from inorganic phosphates; also that the animal has the power to synthesize the purin bases necessary for its nuclein formation from some complexes contained in the protein molecule, and does not necessarily use purin bases of exogenous origin for this purpose. McCollum also placed much emphasis on the idea of palatability as of vital importance in nutrition.

Rats 1, 2 and 3 were fed a normal ration, and gained in weight one gram or more per day. Rats 4, 5 and 6 were fed on the organic-phosphorus-free ration and lost weight rapidly. Rats 7, 8 and 9 received the same ration as the above, but, in addition, protein-free hydrolyzed beef and liver. Rats 8 and 9 lost 27 and 28 grams, respectively, in 106 days. Rat 7 gained 23 grams in 53 days. It was put into the experiment on June 12, weighing 153 grams. By June 23 it weighed 168 grams. On July 28, thirty-five days later, it weighed 170 grams, though between these dates it had weighed as much as 180 grams. On Aug. 4 it was removed from the experiment at a weight of 176 grams. Thus far, then, five out of six rats had failed to maintain their weight; the sixth had made a gain in weight.

Rats 18, 19 and 20 were younger than those used thus far. They were fed on the same ration as rats 4, 5 and 6, that is, without organic phosphorus. They all gained in weight. At the beginning of the test they weighed 37, 35 and 46 grams. In 127, 56

and 56 days, respectively, they gained 39, 6 and 14 grams, respectively, in weight. The one rat which more than doubled its weight was analyzed, along with certain others, for dry substance in the body, fat in the dry matter, and weight and ash of skeleton. (See table below.)

Two rats, Nos. 15 and 16, were fed on the same ration plus casein, and gained in weight without difficulty.

COMPOSITION OF RATS USED IN EXPERIMENTS WITH VARIOUS RATIONS

Ration	Number of rat	Weight	Skeleton	Dry tissues less skeleton	Ether extract	Ash of skeleton	Skeleton	Fat- and water-free tissues
		Grams	Grams	Grams	Grams	Grams	Percent of live weight	Percent of live weight
Normal	1	147	6.67	38.0	8.89	3.79	4.54	19.8
Normal	2	157	6.50	45.0	10.80	3.85	4.14	21.79
Normal	10	34	1.33	9.5	3.25	0.68	3.91	18.39
Inorganic phosphorus later phosphorus-free	7	102	7.14	25.5	3.42	4.49	7.00	21.64
Inorganic phosphorus	4	135	9.00	34.8	7.00	4.28	6.66	20.59
" "	5	96	5.78	22.0	4.01	3.02	6.02	18.94
" "	6	88	7.50	20.5	3.63	3.18	8.52	19.17
" "	8	103	6.03	21.5	2.67	3.52	5.85	18.28
" "	9	78	4.58	14.5	0.86	2.77	5.79	17.49
" "	18	76	4.07	17.5	3.40	2.14	5.36	18.55

By comparing the figures from No. 18, the one rat which doubled its weight, with those from Nos. 1 and 2, which were fed on normal foods, one may satisfy himself by computation that the gain in weight of this one rat could not be made up entirely of fat, water, intestinal content and skeleton. The extent to which the gain in weight was dependent on translocation of constituents was not determined. There were no determinations of moisture in the tissues, nor of nuclein or lecithin phosphorus, and there were no weights of foods taken. The author states in a letter that there was opportunity for the rats to eat their own feces, a fact which we have found enters in most important ways into the determination of results in such work, apparently first through allowing of repeated use of the lecithin of the bile residues, and second through allowing the animal to avail itself of results of the synthetic capacities of intestinal bacteria.

The nature of the analytical data hardly warrants the author's assumption that constancy of composition of the tissues was maintained, and his reference to the work of Hart, McCollum and Fuller with swine, as sustaining the assumption, is not convincing.

One rat was so confined that the excreta could be collected, and a ration was given it of phosphorus-free foods. The amounts eaten were not determined. As an average of 8 days' excretion,

terminating four days before the death of the rat, the author submits the figure 0.0063 gm. phosphorus as the daily elimination of this rat, which weighed 180 gm. at its maximum, and 102 gm. at its death. With this figure as a basis, the author computes that during the course of his experiments certain rats must have entirely changed the phosphorus content of the body, *the skeleton excepted.* He assumes that the rats did not draw phosphorus from the bones from the fact that the skeletons increased in weight, while the animals lost in weight; but there was no evidence presented to show that there was not withdrawal of organic phosphorus from the skeleton coincident with the deposit of inorganic phosphates.

The general failure of the older rats even to maintain live weight on the organic-phosphorus-free diet, taken together with the ability of the younger rats to gain in weight on this ration, implies either that the older animals did not eat food enough, or else that the ability of the rat to gain in weight on rations which are free from organic phosphorus compounds, if possessed at an early age, becomes less marked with advance in age.

Gregersen (1911) conducted an extensive series of balance experiments with rats, the object being to study phosphorus metabolism, especially the possibility of the synthesis of organic phosphorus compounds from phosphorus-free edestin and inorganic phosphates. The work includes in all 48 experiments involving 170 balances. The method of handling the rats was that of Henriques and Hansen (Zeitschr. physiol. Chem., 1905, XLIII, 418). The data reported include analyses of food, urine and feces, but no analyses of the rats themselves. The author's tables have been transcribed without material change but for the omission of the separate urine and feces data. His last table we have omitted.

Gregersen concludes that the organism is able to synthesize organic phosphorus compounds from phosphorus-free organic materials and phosphates; in feeding on a nitrogen-free ration the organism is not affected by the presence or absence of phosphates; when the organism is held in nitrogenous equilibrium on a phosphorus-free albumin-containing ration, the excretion of phosphorus falls off quite considerably, under some circumstances becoming as low as 1/50—1/60 the amount of the coincident nitrogen excretion; on a phosphorus-free, albumin-containing ration, which contains calcium and magnesium salts, the rats excrete only a minimum amount of phosphorus through the urine, less than one-tenth of that quantity which is at the same time excreted in the feces; on a phospho-

rus-free ration containing albumin but no calcium or magnesium salts more phosphorus is usually excreted through the urine than through the feces, likewise on a phosphorus-free albumin-free diet which contains calcium and magnesium. It is not claimed that phosphorus-free nitrogenous compounds and phosphates are of equal value with phosphorized nitrogenous compounds.

From a superficial inspection of the data one is inclined to agree with Gregersen's conclusion as to the synthesis of organic phosphorus compounds, and the facts may be as concluded by Gregersen, but, considering the mass of conflicting testimony which has been reported on this subject, we must weigh the evidence with care. In certain respects the proof of organic phosphorus synthesis appears incomplete or imperfect. There were a great number of experiments; but the periods were very short. The data would be much more satisfactory if they included determinations of the amounts of organic and inorganic phosphorus in the bodies of the experimental animals and in controls. Our knowledge of the capabilities of the animal to transfer and to transform phosphorus from one tissue or compound to another, under the stress of necessity, is too limited to warrant unreserved statements as to synthesis of individual compounds when such deductions rest upon only the storage of the nutrient and gain in live weight during periods of a very few days. Regarding certain points one is left in doubt since the percentage composition of the salt mixtures was not stated.

Turning to Table I, p. 335, these rats were taken from a bread diet, and, without an intermediate period on the experimental ration to free them from the effects of the ration of white bread, but after a fast from one afternoon until 9:00 o'clock next morning, were put into the balance experiments, in which an abundance of protein in the form of edestin, and of phosphorus in the shape of phosphates, were provided. Now bread is deficient in protein and in phosphorus, and extremely low in calcium, so low that it could hardly have failed, with these growing rats, to have caused a loss of calcium, and therefore probably also of phosphorus, from the bones, if indeed the rats received nothing but bread. The abrupt change to the experimental ration found the rats much in need of the protein, calcium and phosphorus which this ration provided, and there was consequently, for a short time, a marked storage of these constituents. This apparent prosperity, however, was not sustained.

TABLE I. METABOLISM EXPERIMENTS ON GROWING RATS ON A DIET CONTAINING NO ORGANIC PHOSPHORUS—Daily Balances

No. of investigation and weight of subject in grams	Length of period in days	Food per day Grams	Food N Milligrams	Food P Milligrams	N balance Milligrams	P balance Milligrams	N:P retained
1 26	5	2.76	71	9.7	23	3.5	6.6
1 28	5	2.04	52	7.2	6	1.4	4.3
2 36	5	3.59	92	12.6	32	4.8	6.7
2 38	5	2.58	66	9.1	10	2.3	4.3
2 38	5	2.58	66	9.1	4	2.1	1.9
3 49	4	5.20	134	18.3	42	7.1	5.9
3 54	4	4.70	121	16.5	17	2.6	6.5
3 55	5	3.71	95	13.1	6	2.2	2.7
4 43	4	4.95	127	17.4	42	7.3	5.8
4 48	4	3.56	91	12.5	20	2.5	8.0
4 49	5	2.85	73	10.0	10	1.5	6.7
4 50	5	2.02	52	7.1	—24	—1.4	
4 45	5	2.48	64	8.7	—11	0.0	
5 44	5	4.12	106	14.5	31	6.1	5.1
5 50	5	3.51	90	12.4	12	1.8	6.7
5 51	5	2.92	75	10.3	— 4	—0.5	
6 63	6	4.57	117	16.1	35	3.9	9.0
6 71	6	3.21	83	11.3	3	1.3	2.3
6 66	6	3.19	82	11.2	1	1.2	0.8
6 65	6	2.91	75	10.2	3	1.9	1.6
7 60	5	4.96	128	17.4	30	4.0	7.5
7 68	6	2.92	75	10.3	— 7	0.3	
7 62	6	3.47	89	12.2	2	0.9	2.2
7 62	6	2.85	73	10.0	—10	0.5	
8 58	6	5.38	138	18.9	37	4.3	8.6
8 63	7	4.50	116	15.8	26	4.6	5.7
8 68	7	3.83	98	13.5	6	3.3	1.8

The ration was composed of edestin 15 percent, sugar 30 percent, fat 42 percent, cellulose 5 percent, sodium phosphate 4 percent, and 4 percent of a salt mixture containing sodium, potassium, and calcium chlorides, sodium bicarbonate, magnesium oxide and iron sulphate.

In these 8 series of balances there was in each case a progressive decline in the food consumed, and in the nitrogen and phosphorus storage. These 8 experiments were 10-24 days in length. Three out of the 8 showed minus nitrogen balances, one in the period composed of the 13th-18th days, another during the 10th-15th days, and the third during the 5th-11th days. Two of these minus nitrogen balances were accompanied by negative phosphorus balances, and in the third the positive balance was but 0.0003 gm. In 6 cases out of the 8 there was a progressive decrease in the proportion of nitrogen to phosphorus stored, at the same time that the storage of both elements also declined, as above noted.

The daily nitrogen storage in the first period of 4-6 days was 23-42 mg.; during the second period the storage was from —7 to +0.26 mg., and in the third period from —4 to +10 mg. The phosphorus storage in the first period was from 3.5 to 7.3 mg., in the second, 0.3 to 4.6 mg., and in the third from —0.5 to +3.3 mg.

These facts are probably due to the falling off in food consumption, which, of course, would leave the rat with a smaller amount of protein, in excess of the maintenance requirement, available for storage, and also a smaller *proportion* of the total protein. The above-mentioned decrease in food consumption, if accompanied by a considerable storage of phosphorus in the bones might then account for the decreased proportion of nitrogen to phosphorus which was stored. In this connection we would observe that the palatability of a ration is very commonly a reflection of the usefulness of the food to the animal.

The general results of this first series of balance experiments suggest great difficulty in the maintenance of normal conditions of growth. This test is the most thoroughgoing of any in the whole investigation, in that the periods were much longer than in subsequent series; also the rats were young, growing animals, and therefore had less reserve material within the body with which to bridge over temporary nutritional deficiencies.

In Table II, p. 337, we have the second series of experiments. The periods were of three to five days duration. Here we have grown rats, fed with and without protein, and without organic phosphorus compounds. The nitrogen-free ration was composed of sugar, lard, cellulose and salts, including sodium phosphate. The ration containing protein was composed like the above, except for the substitution of edestin for 15 percent of sugar. The albumin-free ration was the same as the nitrogen-free ration, except for the addition of 3 percent of Liebig's extract of beef.

In Experiments 9-22 there are 18 changes, either from a nitrogen-free ration, or from one in which the only nitrogen present was in meat extractives, to a ration where the sole albuminous nitrogen present was in edestin, or changes in the reverse direction. Sodium phosphate was present in all rations whether containing protein or without protein. In each of these 18 changes of food the nitrogen and phosphorus balances changed consistently from + to —, or from — to +, according to whether or not edestin was present; that is, there was in every case a storage of both nitrogen and phosphorus in the presence of edestin, and in no case a storage of either element in the absence of edestin, even though the phosphorus was present in greater amount than when edestin was present.

The loss of phosphorus during albumin-free periods was probably due to the katabolism of nitrogenous tissues which contained phosphorus. Then with the introduction of edestin into the ration, the phosphorus-containing proteins were protected, and there occurred both nitrogen and phosphorus retention. One can only speculate as to the form in which the phosphorus was retained. The

average daily loss of P on the nitrogen-free diet during the whole series was 7.0 mg. The daily retention on the edestin ration averaged 2.3 mg. There was not conspicuous uniformity in the ratio of nitrogen to phosphorus either in the loss or the retention of these elements.

TABLE II. METABOLISM EXPERIMENTS ON MATURE RATS WITH AND WITHOUT PROTEIN AND WITHOUT ORGANIC PHOSPHORUS—Daily Balances

No. of investigation, and weight of subject in grams		Length of period in days	Food per day Grams	Food N Milligrams	Food P Milligrams	N balance Milligrams	P balance Milligrams	N:P retained or lost	Ration
9	101	3	7.53	0	26.4	−63	−4.7	13.4	N-free
9	107	3	7.53	197	26.6	61	2.9	21.0	Edestin
10	239	3	10.00	0	35.0	−137	−12.5	11.0	N-free
10	224	3	10.00	261	35.3	14	0.9	15.6	Edestin
10	228	3	8.50	0	29.8	−107	−9.0	11.9	N-free
11	152	3	10.00	0	35.0	−107	−7.3	14.7	N-free
11	146	3	7.80	204	27.5	33	2.0	16.5	Edestin
12	195	3	9.00	0	31.5	−81	−6.1	13.3	N-free
12	188	3	9.00	235	31.8	51	4.6	11.1	Edestin
12	196	3	9.00	0	31.5	−77	−4.4	17.5	N-free
13	125	3	6.50	0	22.8	−59	−6.6	8.9	N-free
13	116	4	5.69	149	20.1	23	2.0	11.5	Edestin
14	138	3	6.00	0	21.0	−57	−4.9	11.6	N-free
14	131	3	6.00	157	21.2	17	0.8	21.4	Edestin
14	137	3	7.00	0	24.5	−57	−2.1	27.1	N-free
14	136	3	5.67	148	20.0	26	1.3	20.0	Edestin
15	160	3	8.00	0	28.0	−63	−6.0	10.5	N-free
15	157	4	6.14	160	21.7	27	2.4	11.3	Edestin
16	58	3	3.50	0	11.5	−44	−3.6	12.2	N-free
16	55	4	3.50	91	11.6	18	2.2	8.2	Edestin
17	58	3	3.55	0	11.7	−45	−4.7	9.6	N-free
17	55	4	3.18	83	10 5	13	1.8	7.2	Edestin
18	72	3	5.00	0	16.5	−37	−2.0	18.5	N-free
18	72	4	2.93	76	9.7	1	0.3	3.3	Edestin
19	290	2	12.00	40	49.7	−171	−16.2	10.6	Albumin-free
19	283	1	12.00	304	39.3				
19	288	3	12.00	304	39.3	42	5.1	8.3	Edestin
19	307	1	12.00	304	39.3				
20	175	2	8.00	26	33.1	−107	−8.9	12.0	Albumin-free
20	169	1	8.00	202	26.2				
20	172	2	8.00	202	26.2	17	0.7	26.4	Edestin
20	174	1	8.00	202	26.2				
21	320	2	12.00	40	49.7	−133	−12.0	11.1	Albumin-free
21	317	1	12.00	304	39.3				
21	322	3	12.00	304	39.3	51	3.5	14.4	Edestin
21	335	1	12.00	304	39.3				
22	247	2	11.00	36	45.5	−108	−8.0	13.5	Albumin-free
22	244	1	11.00	278	36.0				
22	251	2	11.00	278	36.0	49	4.5	10.9	Edestin
22	262	2	11.00	278	36.0				

The nitrogen-free ration was composed as follows: Sugar 45 percent, lard 42 percent, cellulose 5 percent, and salts, including sodium phosphate, 8 percent.

The edestin ration was composed as above except that 15 percent of sugar was replaced by edestin.

The albumin-free ration was composed like the above nitrogen-free ration except for the addition of 3 percent of Liebig's beef extract.

The experiments in Table III (below) compare powdered beef and sodium phosphate with edestin and sodium phosphate. In this series the edestin period in every case follows immediately after a meat period, without intermediate feeding, certain residua from the meat feeding doubtless holding over into the edestin periods in such way as to mix results, and to favor the utilization of the edestin rations. This advantage was increased by the fact that the preliminary meat period was 10-14 days long, the balances covering, on an average, the last 8.3 days of this period, while the following edestin periods were, on an average, only 3.8 days long. In spite of these manifest advantages to the edestin rations, the meat rations made a slightly better showing in the phosphorus balances.

TABLE III. METABOLISM EXPERIMENTS WITH GROWN RATS COMPARING POWDERED BEEF WITH EDESTIN—Daily Balances

No. of investigation, and weight of subject in grams	Length of period in days	Food per day Grams	Food N Milligrams	Food P Milligrams	N balance Milligrams	P balance Milligrams	N:P retained	Ration
23 191	2	7	181	22.8	..	2.5	....	Flesh
23 187	2	7	181	22.8	18	1.3	....	
23 190	3	7	181	22.8	30	2.5	12.0	
23 192	3	7	181	22.8				
23 191	1	6.93	181	23.1	17	1.0	17.0	Edestin
23 194	3	6.93	181	23.1				
24 161	2	6.0	155	19.5	..	0.1	....	Flesh
24 158	2	6.0	155	19.5	3	...	....	
24 158	3	6.0	155	19.5		...	....	
24 158	1	5.94	156	19.8	8	...	....	Edestin
24 161	3	5.94	156	19.8		...	....	
25 122	2	5.00	129	16.3	..	—2.0	....	Flesh
25 120	2	5.00	129	16.3	—7	—0.4	....	
25 121	3	5.00	129	16.3	8	0.8	10.0	
25 123	3	5.00	129	16.3				
25 122	1	4.95	130	16.5	15	0.8	18.8	Edestin
25 121	3	4.95	130	16.5				
25 122	4	5.00	129	16.3	18	0.5	36.0	Flesh
26 195	3	7.00	179	22.7	—8	1.5	...	Flesh
26 188	3	7.00	179	22.7	—3	1.9	....	
26 186	3	6.93	180	22.8	—7	1.2	....	Edestin
27 138	4	5.50	140	18.1	—10	1.0	....	Flesh
27 138	4	5.50	140	18.1	—7	1.3	....	
27 136	3	5.45	141	18.0	—5	0.5	....	Edestin
28 124	4	5.50	140	18.1	—14	3.3	....	Flesh
28 124	3	5.50	140	18.1	—13	3.1	....	
28 123	5	5.45	141	18.0	—11	1.0	....	Edestin

The flesh ration was composed as follows: Powdered beef 20 parts, sugar 25 parts, lard 44.5 parts, cellulose 5 parts, sodium phosphate 2 parts and salt mixture 3.5 parts.

The edestin ration was composed as follows: Edestin 14.93 parts, sugar 25 parts, lard 46.8 parts, cellulose 5 parts, sodium phosphate 3.76 parts and salt mixture 3.5 parts.

The two rations had like calorific value and like content of nitrogen, phosphorus, fat, cellulose and salts.

In Table IV, p. 339, we have a continuance of the tests reported in the preceding table except that the food per gram of live weight of the edestin rats was intentionally increased by the addition of a certain amount of fat to the ration, the object being to determine if

with sufficient calorific value the ration free from organic phosphorus would cause more phosphorus retention than the ration containing organic phosphorus. Gregersen does not mention the coincident reduction in the amount of food eaten per gram of live weight in the meat periods. The food per gram of live weight of the rats on the flesh ration was in this series one gram per 28.4 grams of live weight, while in the preceding series this ration was eaten in the amount of one gram per 25.9 grams of live weight. With these advantages, together with those of influence of previous feeding and shorter duration of the edestin periods, as previously noted, the ration which was free from organic phosphorus appeared to make a better showing in the nitrogen and phosphorus balances than did the flesh ration. The length of the meat period was in each case 12 days, during the last 6 of which balances were taken, and of the succeeding edestin period the average length was 3.7 days. There were, therefore, four differences of experimental conditions between the two rations compared, differences as to calorific value of the rations, as to length of the experimental period, as to advantage from previous feeding, and as to nature of the phosphorus compounds present; which of course makes it impossible to say what factor has produced the differences in results.

TABLE IV. METABOLISM EXPERIMENTS ON GROWN RATS COMPARING POWDERED BEEF WITH EDESTIN

Daily Balances

No. of investigation, and weight of subject in grams		Length of period in days	Food per day Grams	Food N Milligrams	Food P Milligrams	N balance Milligrams	P balance Milligrams	Ration
29	212	6	8	268	29.9	−35	−2.5	Flesh
29	210	1	8+1	267	29.4			
29	220	2	8+2	267	29.4	33	2.2	Edestin + fat
29	220	1	6.8+1	227	24.9			
29	220	2	8	268	29.9			
29	219	2	8	268	29.9	−1.0	0.1	Flesh
30	307	6	10	335	37.4	8.0	1.5	Flesh
30	313	1	10+2	334	36.7			
30	315	2	10+2	334	36.7	52	4.5	Edestin + fat
30	329	1	10+3	334	36.7			
30	336	4	10	335	37.4	10	1.9	Flesh
31	220	6	8	268	29.9	1	−1.6	Flesh
31	226	1	8+1	267	29.4			
31	232	2	8+1.5	267	29.4	7	0.3	Edestin + fat
31	237	3	8	268	29.9			
31	238	2	8	268	29.9	−6	−1.3	Flesh

The flesh ration was composed as follows: Powdered beef 25 parts, sugar 25 parts, lard 40 parts, cellulose 5 parts, sodium phosphate 2 parts and salt mixture 3 parts.

The edestin ration was composed as above except that edestin and sodium phosphate replaced the powdered beef, the nitrogen and phosphorus of the two rations thus being held alike, but in addition the edestin ration contained 1-3 gm. of lard in excess of the amount present in the flesh ration.

Table V, below, sets forth results of a comparison of nitrogen-free, phosphorus-free rations with nitrogen-free, phosphorus-containing rations, the phosphorus in these latter rations being present exclusively as phosphates. The loss of nitrogen and phosphorus, and the proportion of nitrogen to phosphorus in the loss, was not affected by the differences in these rations.

TABLE V. METABOLISM EXPERIMENTS WITH MATURE RATS ON NITROGEN-FREE RATIONS WITH AND WITHOUT PHOSPHORUS

Daily Balances

No. of investigation	No. and weight of subject in grams	Length of period in days	Food per day Grams	Food N Milligrams	Food P Milligrams	N balance Milligrams	P balance Milligrams	N:P retained or lost	Ration
				0					
32	138	3	4	0	0	−68	−6 3	10.8	N-free, P-free
32	135	3	4	0	0	−49	−5.3	9.2	
32	131	3	4	0	0	−49	−4.7	10.4	
32	129	3	4	0	0	−50	−5.0	10.0	
32	124	4	4		0	−48	−4.1	11.7	
				0					
33	207	3	6	0	0	−92	−10.6	8.7	N-free, P-free
33	197	3	6	0	0	−71	−8.2	8.7	
33	189	3	6	0	0	−75	−7.1	10.6	
33	180	3	6	0	0	−60	−5.3	11 3	
33	177	3	6		0	−60	−4.9	12.2	
				0					
34	225	3	6	0	15.3	−95	−10.2	9.3	N-free, P-containing
34	218	3	6	0	15.3	−76	−6.4	11.9	
34	207	3	6	0	15.3	−77	−7.4	10.4	
34	196	3	6	0	15.3	−66	−6.0	11.0	
34	195	3	6		15.3	−61	−6.6	9.2	
				0					
35	175	3	5.0	0	12.7	−103	−8.9	11.6	P-containing
35	164	3	4.85	0	0	−68	−5.1	13.3	P-free
35	154	3	5.0	0	12.7	−60	−5.2	11.5	P-containing
35	148	3	4.85		0	−55	−4.3	12.8	P-free
				0					
36	217	3	6.0	0	15.3	−114	−10.5	10.9	P-containing
36	205	3	5.82	0	0	−81	−6.8	11.9	P-free
36	194	3	6.0	0	15.3	−72	−6.7	10.7	P-containing
36	189	3	5.82		0	−65	−6.3	10.3	P-free
				0					
37	167	3	4.85	0	0	−97	−9.1	10.7	P-free
37	157	3	5.0	0	12.7	−74	−5.5	13.5	P-containing
37	143	3	4.85	0	0	−69	−5.4	12.8	P-free
37	138	3	5.0		12.7	−64	−4.8	13.3	P-containing
				0					
38	202	3	5.82	0	0	−99	−9.4	10.5	P-free
38	191	3	6.0	0	15.3	−70	−6.1	11.5	P-containing
38	182	3	5.82		0	−64	−5.1	12.5	P-free
38	171	3	6.0	0	15.3	−62	−3.8	16.3	P-containing

Nitrogen-free, phosphorus-free ration of investigations 35-38 composed as follows: Sugar 50 parts, lard 42 parts, cellulose 5 parts and salt mixture 3 parts.

Nitrogen-free phosphorus-containing ration of investigations 35-38, the same as above except for the addition of 3 parts sodium phosphate.

Gregersen also presents results of a comparison of nitrogen and phosphorus balances on phosphorus-free rations with and without edestin, and, further, results of a study of the effects of calcium and magnesium salts and sodium carbonate added to the phosphorus-free edestin ration, on the elimination of phosphorus. In the former experiment the phosphorus loss was about the same, whether edestin was present or not, there being no phosphorus retention on the

nitrogen-free ration. In the latter test the salts above mentioned were also without influence on the phosphorus loss, though the presence of calcium and magnesium in the intestine served to deflect into the feces a considerable portion of the food phosphorus otherwise excreted in the urine, and also of the metabolic phosphorus of the body, as evidenced by the phosphorus content of the feces from a ration free from phosphorus but containing calcium and magnesium.

Considering this set of experiments as a whole, then, the trend of the evidence suggests organic phosphorus synthesis by rats, but, as a demonstration of such synthesis, it must be regarded as not of conclusive character. As above noted Gregersen believes that the rats synthesized organic from inorganic phosphorus compounds, but he is careful not to claim that the inorganic compounds are as efficiently retained as the organic.

Heubner (1911) conducted feeding experiments on young dogs comparing phosphates and lecithin as sources of phosphorus for the growing organism. The dogs had been kept on a low-phosphorus diet until their need for phosphorus was acute. Lecithin appeared much superior to phosphates as a source of phosphorus for growing dogs.

Shackell (1911) studied phosphorus metabolism in the early cleavage of the echinoderm egg. He found no evidence of a synthesis of nuclear material from alcohol-soluble constituents of the cytoplasm between the 2-4 celled stage and the blastula stage.

Fingerling (1912a) demonstrated that ducks, on a ration which is low in organic phosphorus, produce eggs of normal content of lecithin and nuclein phosphorus. He concludes that the animal organism possesses the ability to cover its requirement of phosphoric acid for the formation of lecithin and nuclein substances just as easily and completely with inorganic phosphates as with organic phosphorus compounds.

This conclusion could be justified, in so positive a form, only by the use of a ration *free* from organic phosphorus, and by demonstrating with this ration that the original content of the body and of its parts was maintained without loss of organic phosphorus.

J. L. Smith and W. Mair (1912) studied the development of lipoids in the brain of the dog. With reference to the origin of the phosphatid, cerebrosid and cholesterin of the brain they conclude, from the very low content of the mother's milk in these compounds, in connection with the considerable daily deposition of the same in the brain of the suckling (0.045 gm. phosphatid, 0.007 gm. cerebrosid and 0.015 gm. cholesterin), that these compounds are synthesized from other substances present in the milk.

McCollum, Halpin and Drescher (1912) studied lecithin synthesis in the hen, by feeding a ration which was very low in lecithin, and determining the lecithin content of the yolks of the eggs laid. The hens also were weighed. The hens were kept from Oct. 31 until April 15 on a ration containing 30 percent of skim milk powder and 70 percent of polished rice which had been twice extracted in boiling alcohol for 20-30 minutes. From Oct. 31 until Jan. 30 the three hens had gained, respectively, 1290, 2013 and 1588 grams, or 33, 36.4 and 34.1 percent in live weight. They were assumed not to have lost lecithin during this time, or later while laying eggs. During the time from Jan. 30 to April 15 fifty-seven eggs were laid. Their yolks contained 27.65 gm. of phosphorized fats per hen. The food consumption from Oct. 31 until March 1 averaged 58.5 grams per hen per day. The amount of food consumed during the last 45 of the 70 days during which the eggs were laid was not stated.

The proof of synthesis of lecithin from the various phosphorized proteins of the rice and milk would be more complete if the authors had made determinations of lecithin in the bodies of the hens, and in controls, and had submitted quantitative determinations of the lecithin in the foods, since they were not said to be entirely lecithin-free.

Masslow (1913a, b, c) studied the biological significance of phosphorus for the growing organism by means of feeding, metabolism, tissue analysis and enzyme estimation experiments on young dogs. Normal feeding was compared with feeding on a phosphorus-poor diet, and with feeding on phosphorus-poor food plus phosphates, glycerophosphates and lecithin. Casein and albumin were also compared.

The phosphorus-poor diet led to emaciation and finally death, the phosphorus content of the organs having diminished. This loss of phosphorus was mainly inorganic. Of the organic phosphorus only the lipoid compounds decreased. The brain and heart appeared not to lose phosphorus, the loss being greatest in liver, intestines, muscles, bone marrow and kidneys. The ferment functions of the organs was markedly disturbed, the depression of the action of lipase, amylase and diastase being especially great, there being also a like tendency as to catalase and nuclease. In these respects the liver suffers most, the brain and heart comparatively little.

The addition of inorganic phosphates and glycerophosphates to the low-phosphorus diet did not prevent phosphorus impoverishment. Lecithin, however, caused an enriching of the organism in phosphorus, especially in organic compounds other than lecithin. The improvement took place especially in the visceral organs. The ferments were stimulated to greater activity.

Exclusive milk diet, maintained beyond the normal period for such food, led to disturbances of the enzyme activity and phosphorus compounds of the tissues similar to those produced by the low-phosphorus diet.

Fingerling (1913) fed to goats rations of straw, blood, nuclein, starch, molasses and oil, with the addition of phytin, lecithin, casein, nuclein, nucleic acid or disodium phosphate. No essential difference was observed in the utilization of phosphorus in the different forms.

Durlach (1913) compared various phosphorus compounds, organic and inorganic, in feeding and balance experiments with young dogs. The basal ration was poor in phosphorus and consisted of cakes made from isolated foodstuffs and inorganic salts. The pups were kept on the mother's milk for 36-38 days; then to bring them to a state of high phosphorus requirement they were kept on the basal ration for 15-22 days, after which time they were given the distinctive diets. Comparisons were made of monosodium and monopotassium phosphates with Merck's ovo-lecithin and with a mixture of monopotassium phosphate, lecithin, sodium phytate, casein and sodium nucleate. All of the dogs lost in weight. Results were not conclusive, but seemed to show lecithin to possess superior nutritive value inasmuch as two of the three dogs which received lecithin were the only ones which survived the experiments.

E. B. Forbes and associates (1914; Ohio Tech. Bul. No. 6) have conducted five series of feeding, metabolism, and carcass analysis experiments, involving 120 growing swine, in the comparison of the nutritive values of several organic and inorganic compounds of phosphorus. The compounds of interest, in the usual "chemically pure" form, were added, in equivalent amounts, to low-phosphorus standard or basal rations composed, in the main, from comparatively simple manufactured products of plant and animal origin. From about 75 tables of results four only are quoted.

Series I, conducted in April and May, 1908, consisted of metabolism experiments with four pigs, comparing phosphates, glycerophosphates, hypophosphites, and nucleic acid from yeast. The phosphates, glycerophosphates, and hypophosphites were mixtures, in each case, of salts of sodium, potassium, calcium, magnesium and iron. The basal ration consisted of pearl hominy (corn minus the skin and the germ), blood albumen, wheat gluten, and salt, with the addition of small amounts of senna when necessary. The experimental periods were 10 days in length.

That phosphorus in each form was absorbed and retained is unquestionably true, even the hypophosphites increasing the urinary phosphorus and phosphorus retention. Considering normal re-

quirements of calcium for growth, these pigs all suffered from a deficient intake of this element. Conditions were not considered favorable for a close comparison of the nutritive values of the phosphorus compounds involved. The condensed balance data are presented in the following table:

BALANCE EXPERIMENTS WITH GROWING SWINE, COMPARING PHOSPHORUS COMPOUNDS

Grams per Day—Analyses by H. S. Woods and A. C. Whittier

Series I; 10-day Periods

Pig and period No.	Live weight Initial Final Lbs.	Average daily ration	N Food	N Urine	N Feces	N Balance	S Food	S Urine	S Feces	S Balance	P Food	P Urine	P Feces	P Balance	Ca Food	Ca Urine	Ca Feces	Ca Balance	Mg Food	Mg Urine	Mg Feces	Mg Balance	K Food	K Urine	K Feces	K Balance
1 Period I	81.00 87.75	Hominy	1310.13	26.421	2.255	0.671	0.277	0.287	0.719																	
		Blood albumen	40.25	17.094	1.169	0.026	0.177	0.068	0.164																	
		Wheat gluten	40.25	1.662	0.203	0.309	0.142	0.121	0.274																	
		Senna	2.40	+7.665	+0.883	+0.336	−0.042	+0.098	+0.281																	
1 Period II	88.25 99.25	Hominy	1314.71	26.720	2.272	1.287	0.251	0.296	1.114																	
		Blood albumen	41.32	17.078	1.248	0.435	0.001	0.045	0.185																	
		Wheat gluten	41.32	1.175	0.153	0.205	0.074	0.087	0.238																	
		Senna	1.00	+8.467	+0.871	+0.647	+0.176	+0.164	+0.691																	
		Phosphates..(P)	0.613																							
1 Period III	100.75 109.00	Hominy	1245.63	25.263	2.149	1.210	0.206	0.273	1.042																	
		Blood albumen	39.03	16.084	1.138	0.464	0.005	0.059	0.310																	
		Wheat gluten	39.03	1.150	0 164	0.235	0.070	0.102	0.262																	
		Phosphates..(P)	0.573	+8.029	+0.847	+0.511	+0.131	+0.112	+0.470																	
2 Period I	84.50 92.25	Hominy	1383.30	27.621	2.365	0.706	0.286	0.302	0.754																	
		Blood albumen	41.44	18.405	1.337	0.021	0.077	0.078	0.132																	
		Wheat gluten	41.44	1.506	0.198	0.268	0.160	0.115	0.226																	
		Senna	2.40	+7.710	+0.830	+0.417	+0.049	+0.109	+0.396																	
2 Period II	92.75 102.50	Hominy	1389.38	29.292	2.399	1.332	0.285	0.343	0.814																	
		Blood albumen	43.40	18.825	1.370	0.341	0.004	0.071	0.298																	
		Wheat gluten	43.40	1.153	0.148	0.217	0.089	0.123	0.234																	
		Senna	2.00	+9.314	+0.881	+0.774	+0.192	+0.149	+0.282																	
		Nucleic acid..(P)	0.619																							
2 Period III	104.25 112.25	Hominy	1288.13	27.153	2.223	1.232	0.216	0.307	0.739																	
		Blood albumen	40.39	17.778	1.185	0.562	0.009	0.125	0.389																	
		Wheat gluten	40.39	1.149	0.195	0.225	0.073	0.170	0.212																	
		Nucleic acid..(P)	0.574	+8.226	+0.843	+0.445	+0.134	+0.012	+0.138																	
3 Period I	89.50 96.50	Hominy	1451.70	28.773	2.471	0.738	0.303	0.319	0.788																	
		Blood albumen	42.65	18.816	1.386	0.022	0.154	0.090	0.178																	
		Wheat gluten	42.70	2.383	0.227	0.262	0.110	0.125	0.194																	
		Senna	2.40	+7.874	+0.858	+0.454	+0.039	+0.104	+0.416																	
3 Period II	97.25 109.25	Hominy	1435.19	29.057	2.478	1.384	0.320	0.326	1.063																	
		Blood albumen	44.50	18.237	1.327	0.630	0.006	0.061	0.173																	
		Wheat gluten	44.50	1.359	0.167	0.175	0.068	0.122	0.197																	
		Senna	3.00	+9.461	+0.984	+0.579	+0.246	+0.143	+0.693																	
		Hypophosphites..(P)	0.648																							
4 Period I	90.25 99.75	Hominy	1501.13	29.563	2.545	0.760	0.287	0.323	0.809																	
		Wheat gluten	43.44	19.245	1.360	0.019	0.162	0.096	0.131																	
		Blood albumen	43.44	2.137	0.229	0.344	0.184	0.125	0.493																	
		Senna	1.90	+8.181	+0.956	+0.397	−0.059	+0.102	+0.185																	
4 Period II	100.38 107.00	Hominy	1276.66	25.974	2.208	1.265	0.295	0.575	1.138																	
		Blood albumen	40.14	18.094	1.349	0.225	0.008	0.119	0.116																	
		Wheat gluten	40.14	1.765	0.220	0.368	0.140	0.236	0.330																	
		Senna	2.00	+6.115	+0.639	+0.672	+0.147	+0.220	+0.692																	
		Glycerophosphates	0.609																							

Series II, conducted in November and December 1908, consisted of a feeding and carcass analysis experiment, covering 56 days, and involving the use of 30 pigs, five individuals in each of six lots. The basal ration was composed of pearl hominy, blood albumen, wheat gluten, and corn bran. Salt was allowed *ad libitum*. Corn meal and chalk were introduced into the diet at certain times, for corrective purposes. The phosphorus compounds compared were the same as in Series I. The several lots received rations as follows:

Lot 1, basal ration plus hypophosphites
Lot 2, basal ration plus hypophosphites and nucleic acid
Lot 3, basal ration plus glycerophosphates
Lot 4, basal ration plus phosphates
Lot 5, basal ration alone
Lot 6, check lot, killed at beginning of experiment

The pigs in lots 1 and 2 suffered from great weakness and lameness; they were also subject to indigestion. The legs were weak, especially the hind ones, which trembled, and bowed out, and the feet were set far under the body. The fore feet were also sore. The muscular control was poor, and difficulty was experienced in stepping up 6 inches onto the feeding platform. These pigs lay down most of the time, and if disturbed would at once lie down again. They ate well, but moved slowly, carefully and without spirit. Lot 5, which received no phosphorus supplement, behaved much as did lots 1 and 2, but the abnormal tendencies were less pronounced. Lot 3, receiving glycerophosphates, were entirely normal; they ran and played in the best of spirits. Lot 4, receiving phosphates, also remained in good condition, though they were less active than the pigs receiving glycerophosphates.

Considerable difficulty was experienced in the management of the feeding, the lots receiving hypophosphites and nucleic acid requiring frequent reduction in the amount of food given, and in the amount of the phosphorus supplements. These reductions it was not possible to make up by subsequent increase. On these accounts the food consumption could not be maintained uniform in all lots, a fact which resulted in certain advantage to the pigs receiving glycerophosphates. The nutritional disorders in certain lots, as above noted, were successfully combatted by the feeding of limited amounts of corn, which in this relation appeared to possess marked curative value, perhaps due to its organic phosphorus compounds—perhaps to vitamines. The basal ration, by the way, was very poor in fats.

Conclusions as to the effects of the phosphatic supplements were drawn from slaughter weights of parts and organs, and analyses of the hams, brains, livers, kidneys, femora, and tibiae, the data in all cases representing composite samples from the 5 individuals in an experimental lot. For a discussion of the results see p. 352.

Series III, conducted during November and December 1909 and January 1910, was in every way similar to Series II. The feeding covered a period of 70 days, and the experiment involved 35 pigs in 7 lots of 5 each. The basal ration consisted of pearl hominy, wheat gluten, blood albumen, and corn bran. Salt was allowed *ad libitum*. To this basal ration were added, at various times during the experiment, chalk, soda, sugar and corn meal, in efforts to relieve difficulties in the feeding. Without some corn it seemed impossible to keep the pigs in condition for experimentation. The phosphorus compounds fed were the same mixtures used in Series I and II. The several lots received rations as follows:

Lot 1, basal ration plus hypophosphites
Lot 2, basal ration plus nucleic acid
Lot 3, basal ration plus glycerophosphates
Lot 4, basal ration plus phosphates
Lot 5, basal ration plus phytin
Lot 6, basal ration alone
Lot 7, check lot, killed at beginning of experiment.

Difficulties in the feeding were encountered in all lots except the one receiving glycerophosphates, and the one which received no phosphorus supplement. The pigs receiving glycerophosphates were much the most spirited and active of any in the series. Hypophosphites and nucleic acid, when fed in amounts furnishing 2 grams of phosphorus daily to each lot of 5 pigs caused nausea, vomiting, and indigestion. Phytin appeared to cause indigestion, but not pronounced nausea. As a whole the pigs in this series were much less tolerant of the phosphorus compounds fed (other than glycerophosphates) than those in Series II. In this experiment even the pigs receiving orthophosphates exhibited very limited tolerance for the mineral supplement.

Series IV, conducted in November and December 1910 and January 1911, was similar in method to Series II and III, the feeding extending over a period of 70 days, and the experiment involving 45 pigs. The basal ration in lots 1-5 consisted of pearl hominy, wheat gluten, blood albumen, corn bran and agar-agar, salt being allowed

ad libitum. To this ration were added, during portions of the experiment, mangel wurzels and potassium citrate, for corrective purposes. Lots 6-8 received a similar ration, except that corn replaced the pearl hominy used in the food for lots 1-5. The hypophosphites, nucleic acid and phosphates used were mostly of the same lots as those used in the earlier series, but the glycerophosphate mixture was soon exhausted and was then replaced by calcium glycerophosphate alone. The phytin was in part a commercial product, and in part a preparation of the related compound from wheat bran. The several lots received rations as follows:

Lot 1, hominy basal ration alone
Lot 2, hominy basal ration plus nucleic acid
Lot 3, hominy basal ration plus glycerophosphates
Lot 4, hominy basal ration plus phosphates
Lot 5, hominy basal ration plus phytin
Lot 6, corn basal ration plus precipitated bone flour
Lot 7, corn basal ration plus glycerophosphates
Lot 8, corn basal ration alone
Lot 9, check lot; killed at beginning of experiment.

The pigs in this experiment exhibited, in general, the same symptoms as noted with regard to the previous series. The pigs which received nucleic acid and phytin, and those on the hominy basal ration alone, suffered from much weakness and soreness of the feet and legs. There was also considerable trouble with indigestion in these lots, as also in the phosphate lot, and the pigs receiving phytin showed some appearance of nausea. The glycerophosphate pigs, as usual, were entirely normal, and suffered only from the restricted food allowance necessitated by the unsatisfactory behavior of other lots. Lots 1, 2, 4 and 5 ate their own feces; lots 3, 6, 7 and 8 showed no such tendency.

In Series II, III and IV it was necessary, because of digestive disturbance or lack of appetite, to reduce the amount of food allowed to one or more of the experimental lots on 51 dates. The pigs receiving glycerophosphates were not the occasion for any one of these food reductions, their immunity to nutritional disturbance being complete, and in marked contrast to the behavior of all other lots. Each of the other rations contributed in somewhat nearly the same proportion to the occasions for reduction of food allowance.

Series V, conducted during March, April, May and June 1913, was a carefully controlled set of balance experiments comparing glycerophosphates and phosphates, and was terminated by a slaughter test and a complete chemical accounting for the bodies of the experimental subjects. Six barrows, all of the same litter, were

used in this investigation. Two were killed as controls at the beginning of the study, the other four serving as subjects for the metabolism experiments. With the same low-phosphorus basal ration, two pigs received phosphates, and two glycerophosphates, the mineral bases in these supplements being proportioned, one to another, as in sow's milk. The basal ration was composed, as in the earlier studies, from pearl hominy, blood albumen, wheat gluten, corn bran, agar-agar and salt.

As in the previous work, much difficulty was experienced in the feeding of the pigs, other than those receiving glycerophosphates, and frequent readjustment of the level of intake of food was necessary. Very fine grinding, and extensive dilution of the food with water, were tried in efforts to solve the problem of feeding the orthophosphates, but without distinct success. The experiment finally terminated itself in the digestive collapse of one of the pigs receiving phosphates.

A part of the balance data, reduced to amounts per kilogram of live weight, are presented in the following tables:

EXPERIMENTS WITH GROWING SWINE, COMPARING PHOSPHATES AND GLYCEROPHOSPHATES—BALANCE DATA PER KILOGRAM OF LIVE WEIGHT—Grams

Analyses by F. M. Beegle, C. M. Fritz and L. E. Morgan

Series V, Period III, 10 Days

Pig No.	Ave. live weight in Kg.	Average daily rations Total food and supplemental phosphorus	Na Food	Na Urine	Na Feces	Na Balance	K Food	K Urine	K Feces	K Balance	Ca Food	Ca Urine	Ca Feces	Ca Balance	Mg Food	Mg Urine	Mg Feces	Mg Balance	S Food	S Urine	S Feces	S Balance	P Food	P Urine	P Feces	P Balance	Cl Food	Cl Urine	Cl Feces	Cl Balance	N Food	N Urine	N Feces	N Balance
3	70.4	Total food....1208.5	.021	.011	.006	.004	.025	.010	.006	.009	.006	.001	.003	.003	.007	.002	.001	.003	.037	.016	.005	.016	.022	.002	.006	.014	.035	.031	.000	.004	.308	.075	.022	.209
		P. as glycerophosphate.... 0.295																																
4	86.1	Total food....1472.6	.021	.012	.003	.006	.025	.009	.004	.012	.006	.001	.002	.003	.007	.002	.001	.003	.037	.016	.004	.016	.021	.006	.002	.013	.027	.029	.000	—.002	.307	.081	.020	.206
		P. as glycerophosphate.... 0.359																																
5	89.2	Total food....1530.6	.021	.011	.002	.008	.025	.010	.007	.008	.006	.001	.002	.003	.007	.002	.001	.003	.037	.015	.004	.017	.022	.005	.002	.014	.035	.029	.000	.006	.308	.076	.019	.213
		P. as phosphate.... 0.373																																
6	77.0	Total food....1329.3	.021	.015	.003	.003	.025	.006	.003	.015	.006	.000	.003	.003	.007	.002	.001	.003	.037	.016	.004	.017	.022	.006	.002	.013	.035	.030	.000	.005	.310	.083	.017	.210
		P. as phosphate.... 0.324																																

Apparent inconsistencies in balances are due to discarding fractions.

EXPERIMENTS WITH GROWING SWINE, COMPARING PHOSPHATES AND GLYCEROPHOSPHATES—BALANCE DATA PER KILOGRAM OF LIVE WEIGHT—Grams

Analyses by F. M. Beegle, C. M. Fritz and L. E. Morgan

Series V, Period IV, 10 Days

Pig No.	Ave. live weight in Kg.	Average daily rations Total food and supplemental phosphorus		Na	K	Ca	Mg	S	P	Cl	N
3	74.8	Total food 1404.6	Food	.023	.027	.006	.007	.040	.024	.038	.337
			Urine	.008	.009	.000	.002	.016	.003	.029	.079
		P. as glycerophosphate 0.343	Feces	.006	.007	.002	.001	.005	.005	.000	.023
			Balance	.009	.012	.004	.004	.019	.015	.009	.234
4	89.8	Total food 1421.5	Food	.019	.023	.005	.006	.034	.020	.032	.284
			Urine	.017	.005	.001	.002	.015	.006	.027	.074
		P. as glycerophosphate 0.347	Feces	.004	.003	.002	.001	.004	.002	.000	.020
			Balance	—.002	.015	.003	.003	.015	.012	.005	.191
5	93.4	Total food 1474.4	Food	.019	.023	.005	.006	.034	.020	.032	.284
			Urine	.021	.004	.001	.002	.016	.006	.028	.078
		P. as phosphate 0.360	Feces	.001	.006	.002	.001	.004	.002	.000	.021
			Balance	—.003	.013	.003	.003	.013	.012	.004	.185
6	81.6	Total food 1534.0	Food	.023	.027	.006	.007	.040	.024	.038	.338
			Urine	.019	.006	.000	.002	.018	.006	.032	.090
		P. as phosphate 0.374	Feces	.001	.007	.002	.001	.004	.002	.000	.018
			Balance	.002	.014	.004	.004	.018	.015	.006	.230

Apparent inconsistencies in balances are due to discarding fractions.

EXPERIMENTS WITH GROWING SWINE, COMPARING PHOSPHATES AND GLYCEROPHOSPHATES—BALANCE DATA PER KILOGRAM OF LIVE WEIGHT—Grams

Analyses by F. M. Beegle, C. M. Fritz and L. E. Morgan

Series V, Period V, 10 Days

Pig No.	Ave. live weight in Kg.	Average daily rations Total food and supplemental phosphorus		Na	K	Ca	Mg	S	P	Cl	N
3	79.3	Total food 1412.0	Food	.022	.026	.006	.007	.038	.022	.036	.320
			Urine	.009	.004	.000	.002	.016	.003	.029	.078
		P. as glycerophosphate 0.345	Feces	.006	.008	.002	.001	.005	.006	.000	.025
			Balance	.006	.013	.004	.004	.017	.013	.008	.217
4	91.9	Total food 1083.8	Food	.014	.017	.004	.005	.025	.015	.024	.212
			Urine	.007	.007	.000	.002	.012	.005	.020	.059
		P. as glycerophosphate 0.264	Feces	.002	.002	.001	.001	.003	.001	.000	.013
			Balance	.005	.008	.002	.002	.010	.008	.004	.140
5	85.8	Total food 1124.4	Food	.016	.019	.004	.005	.028	.016	.027	.235
			Urine	.008	.005	.000	.002	.013	.006	.021	.060
		P. as phosphate 0.274	Feces	.001	.008	.002	.001	.003	.003	.000	.016
			Balance	.007	.006	.002	.002	.012	.008	.006	.159
6	86.9	Total food 1540.0	Food	.021	.025	.006	.007	.038	.022	.036	.318
			Urine	.013	.005	.000	.002	.018	.007	.028	.079
		P. as phosphate 0.376	Feces	.001	.011	.002	.002	.005	.004	.000	.020
			Balance	.007	.009	.003	.003	.016	.012	.008	.219

Apparent inconsistencies in balances are due to discarding fractions.

Discussion of Results. From the results of Series I it is manifest that orthophosphates, hypophosphites and yeast nucleic acid may all be absorbed by swine, and may be retained in considerable quantity for at least 10 days. That the retention of each of these compounds may be permanent seems altogether probable. In the case of hypophosphites this would involve a further oxidation of the phosphorus to the ortho form.

Under the conditions of Series II, III and IV, there was some evidence to suggest nutritive superiority of glycerophosphates to orthophosphates, nucleic acid, phytin and hypophosphites, especially in relation to the proportion of muscular tissue and fat in the increase, and the breaking strength and ash per cubic centimeter of volume of the bones, but the evidence was not sufficiently of one sort to establish facts with certainty.

It seems quite possible that the amount of exercise taken by the pigs, as determined simply by the state of feeling induced by the phosphorus compounds fed, entirely irrespective of fundamental nutritive effects, may have entered prominently into the determination of the relative development and even the composition of the parts.

The final series of experiments, No. 5, was intended to establish any such fundamental differences as there may be in the nutritive values of phosphates and glycerophosphates. It included complete and protracted mineral and nitrogen balances, complete chemical accounting for the carcasses of the pigs, determinations of digestibility of the food constituents, determinations of the comparative development and composition of various organs and tissues, and daily determinations of the nitrogen, creatinin and ammonia of the urine.

Throughout this exhaustive study there was marked similarity in the results from both rations. Aside from the much greater acceptability of the glycerophosphates than the phosphates there were no differences of note in results from the two pairs of pigs.

The result of this series was a remarkably uniform and consistent set of observations of many sorts indicating that, at least under the artificial conditions of this experiment, there are no essential differences in the fundamental nutritive value of phosphates and glycerophosphates for purposes of growth in swine.

Conclusions. Phosphates, hypophosphites, glycerophosphates, nucleïc acid (from yeast) and phytin are all absorbed and retained, and apparently utilized, by growing swine, when added in the pure form to rations low in phosphorus but capable of maintaining phosphorus equilibrium.

Marked differences were observed in the tolerance of swine toward the several phosphorus compounds used. These were found to compare as to acceptability to swine, when fed in quantities furnishing equal amounts of phosphorus, in the following order, the most acceptable being mentioned first, and the others in order of decreasing acceptability: glycerophosphates, orthophosphates, phytin, nucleic acid and hypophosphites.

That the differences in acceptability of these isolated compounds similarly affect the foodstuffs in which they are naturally combined seems certainly not to be a fact. These differences in acceptability were not found definitely related to more fundamental nutritive effects.

That the particular organic compounds used in this investigation (nucleic acid, phytin and glycerophosphates) have nutritive values, to growing swine, superior to the inorganic compounds used (orthophosphates and hypophosphites) was not shown. No fundamental differences in the nutritive values of the phosphorus compounds studied were established.

No basis, therefore, was discovered for a differentiation between the nutritive values of organic and inorganic phosphorus compounds generally. It should be borne in mind, however, that no representatives of the two classes, phosphoproteins and lecithins, were included in this investigation, and results obtained under conditions of such rigid experimental control may not accurately represent the facts under optimum normal conditions of life. These results are not considered to controvert evidence as to specific therapeutic effects of the same compounds in relations other than those considered in this study.

The amount of phosphorus which an animal will tolerate, when added to the ration in readily soluble form, is definitely limited at an amount much less than that which will be acceptable in its natural relationships in foods.

From the great difficulty experienced in the feeding of yeast nucleic acid and of commercial phytin, as well as the related compound from wheat bran, it is concluded that the isolation of such compounds from natural products alters at least their therapeutic effects in such manner that it becomes impossible to state, from investigations of this sort, on pure compounds, what may be their nutritive values in their natural relationships in common foods.

It seems unlikely that, with growing animals, any ration composed from natural foods, and supplying the nitrogen requirement, will fail to furnish enough phosphorus to maintain phosphorus equi-

librium. That many rations compounded from common foods are lacking in the amount of phosphorus essential to maximum retention and growth, however, is as certainly true.

The addition of comparatively small amounts of corn to rations compounded from simple manufactured products of plant and animal origin may enhance the nutritive value of such rations to an extent out of proportion to the amount of corn added, and may affect the results of such comparisons of phosphorus compounds as are here reported in definite and fundamental ways determined by the state of nutrition of the animal, especially with reference to nutritive reserves, resulting from the previous feeding and life activity.

In spite of a marked tendency toward constancy of composition, appreciable differences were noted in the chemical constitution of the organs and tissues of different experimental lots of swine, these differences apparently being due in part to the phosphorus compounds fed, and in part to other factors which were not controlled.

Such differences in the composition of tissues as were observed might be accounted for as due to variations in the liquid content of the parts, the salts varying accordingly, or to the composition of supporting structures or unorganized nutritive materials.

There is also, in medical literature, a vast amount of clinical evidence to which we could refer, much of it flimsy, it is true, but other portions of undoubted value as showing specific effects of lecithin which are not possessed by phosphates, especially the direct contribution of lecithin to the lecithin content of the blood serum and tissues, and to the increase of the red blood corpuscles.

See summary, p. 534.

ORGANIC PHOSPHORUS SYNTHESIS IN FASTING SALMON

This problem of synthesis of organic phosphorus compounds has also been attacked from another angle in the study of the composition of salmon at different stages of sexual maturity, these fishes, in the journey to their spawning grounds, traveling long distances, apparently without taking food, and at the same time accomplishing the organization of great masses of the sexual elements.

Miescher (1881), in studying the life of the Rhine salmon, came to the conclusion that the very great development of nuclear material in the sexual elements during fast took place at the expense of the muscular system. This investigation was not concluded.

Paton *et al.* (1897-8, 1898) made an extensive series of observations on the metabolism of the salmon during its life in fresh water.

Lecithin was determined from the ether extract; inorganic phosphorus by extraction of the ether-extraction residue with 0.2 per cent hydrochloric acid, while the phosphorus in nuclein and pseudonuclein was determined in the residue from the above-mentioned hydrochloric acid extraction.

The matter of especial interest in this investigation is the evidence on the subject of synthesis of organic phosphorus compounds. By tissue analysis of fishes from the estuary, and later from the upper river waters, after the development of the ovaries and testes during fast, conclusions were drawn as to the transformation of phosphorus compounds within the body. In the female fish the lecithin of the trunk muscles was found to be insufficient to yield the lecithin phosphorus of the ovaries, the total phosphorus lost by the trunk muscles being only just sufficient to yield the total phosphorus laid on by the ovaries; but in the male fish more lecithin is lost from the muscles than is required by the testes.

The authors concluded that the phosphorus stored in the muscles as simple phosphates is transferred to the ovaries and testes, and there built up into organic combinations, lecithin constituting an important step in the conversion of the phosphates into true nuclein in the testes, and into the intermediate pseudonuclein, ichthulin, and, later, true nuclein in the ovaries.

The study of this problem is attended by difficulties which warrant the suspension of our judgment as to the significance of the results at least until there shall have been made complete chemical accountings for the entire bodies of the fishes.

Milroy (1908) has made similar studies on the herring, but definite conclusions were not reached as to the source of the phosphorus compounds of the ovaries and testes.

ADVANTAGE OF COMPLEXITY OF ORGANIZATION IN FOOD PHOSPHORUS

On *a priori* grounds a certain superiority of the organic as compared with the inorganic phosphorus compounds would be considered to be due simply to the greater complexity of organization, since in the case of those compounds (the lecithins and the nucleins) which are absorbed in part as such, or in a state of incomplete digestive cleavage, a certain amount of synthetic activity is probably spared the animal. As to how important a matter this may be we can only speculate. With reference to nitrogen compounds, however, the maintenance of nitrogen equilibrium with the less completely split proteins seems to be appreciably more efficient than

with the products of complete digestive cleavage, and the same principle may be operative in the case of some of the organic phosphorus compounds.

Abderhalden and Rona (1904) found, in experiments with mice, that pancreatic digestion products of casein are about as valuable for maintenance of live weight as casein itself, that the further split products of peptic-pancreatic digestion of casein are of less value, though of some use, while the products of sulphuric acid hydrolysis seemed to be without value. These authors (1905) concluded that a dog was able to utilize pancreatic digestion products of casein, these products consisting of amino acids and complex substances not giving the biuret reaction; but the products of acid hydrolysis of casein were not able to maintain nitrogen equilibrium. In later work, however, Abderhalden (1912) showed, in protracted nitrogen balance experiments, that dogs are able to maintain nitrogen equilibrium and retention on products of either acid or enzymatic splitting of proteins, or on a mixture of recognized amino-acids. Abderhalden expresses the belief that the organism must have prepared for itself all of the building stones which are specific for phosphatids, since these were not fed. To have demonstrated this point, however, would have required carcass analyses, which were not a part of this investigation.

D. D. Van Slyke and G. F. White (1911), in protein digestion and retention experiments with dogs, found that with various meats the rate of digestion and absorption, as indicated by the rate of elimination, was, in general, the reverse of the amount of nitrogen retained from each at the end of 24 hours.

In explanation of these results the authors (Van Slyke and White) suggest that a larger proportion of the more readily digested proteins may be absorbed in the form of the lowest cleavage products, which Carrel, Levene, Meyer and Manson, and also Voit and Zisterer and others, have shown to be less capable than the higher cleavage products to maintain nitrogenous equilibrium.

In the light of these experiments it is quite conceivable that, other things being equal, some of the more highly organized organic phosphorus compounds should possess, on account of their state of organization, nutritive value greater than that of the simplest inorganic phosphates.

A further advantage to the animal in having the phosphorus compounds of the food organically combined is suggested by the experience of one of us (E. B. F.) in the feeding of pure phosphates along with a low-phosphorus basal ration to swine. The ready solu-

bility of the uncombined phosphates results in such a concentration of these salts in the digestive tract as causes nausea or catharsis. Much larger amounts of phosphorus may be utilized in a normal manner if they are gradually liberated in the usual way by the digestive cleavage of the organic complexes with which they are combined.

FEEDING EXPERIMENTS WITH RATS AND MICE ON RATIONS COMPOSED OF SIMPLE PURIFIED NUTRIENTS

An important addition to the evidence on organic phosphorus synthesis has been made through a number of extensive series of feeding experiments with rats and mice, most of them having for their object especially the study of synthesis of nitrogen compounds in general, by experiments on growth and reproduction, on rations of simple purified nutrients.

Röhmann conducted experiments with mice which show that even though phosphoproteins and nucleoproteins be present in abundance, and mineral salts be furnished as phosphates, nitrates, chlorides and lactates of the more important bases in the body, there may still be nutritive deficiencies in the ration such as gradually, through the course of successive generations, make growth impossible.

Röhmann (1902, 1907) successfully reared two generations of mice on an artificial food mixture containing its phosphorus as phosphoprotein, nucleoprotein and phosphates, but failed to rear the third generation. In a later paper (1908) Röhmann reported success in rearing three generations of mice to maturity on artificial foods, but the fourth generation could not be reared. The nutrients used in these experiments were casein, egg albumin, nucleoprotein from liver, potato starch, wheat starch, margarine, malt, chicken protein and a salt mixture compounded as follows:

10 parts calcium phosphate
40 parts acid potassium phosphate
20 parts sodium chloride
15 parts sodium citrate
8 parts magnesium citrate
8 parts calcium lactate

Mendel suggested that Röhmann's final failure was due to deficiency in the salt mixture. Stepp ascribed the limited usefulness of this ration to deficiency of lipoids.

Falta and Noeggerath (1906) attempted to maintain adult white rats on artificial food mixtures and inorganic salts, including

calcium phosphate. Neither the rations containing phosphorus-free proteins nor those containing organic phosphorus, as of casein, would keep the animals alive indefinitely, though controls fed on milk, milk powder or horse flesh throve without incident.

L. Jacob (1906) kept rats as long as 124 days on artificial mixtures of foodstuffs, such as casein, cane sugar, cellulose, hog fat and salts. Doves fed on a similar mixture did not do well, perhaps because the feed formed a soft mass in the crop.

Knapp (1908) records unsuccessful attempts to maintain rats on artificial foods and salts.

Stepp (1909) sought to determine the office of the lipoids of bread, on the growth of mice, by feeding mice on bread extracted with alcohol and ether, or alcohol, ether and chloroform, in comparison with others which received the residue plus the extract. The results were inconclusive; none of the mice throve.

At a later date Stepp (1911) conducted a series of 19 experiments on the growth of mice on various diets with and without the presence of those lipoid bodies which are soluble in alcohol and ether. Maintenance of life and live weight were the criteria on which conclusions were based. Some of the more important results are as follows:

Mice die when fed with food which has been completely freed from lipoids. The length of life is increased if the alcohol-ether soluble constituents are added to the extracted food. Fat plays no significant rôle itself, though there are in butter and in milk-fat very small quantities of important alcohol-ether soluble materials. These substances are present in greater amounts in milk plasma. Lecithin and cholesterin seem not to be the necessary lipoids.

That unknown food constituents may possess properties of much importance, and of a value out of proportion to amount, is indicated by experiments by Hopkins (1912) in the feeding of rats. When added to rations of purified products such as pure casein, starch, cane sugar, lard and salts—a very small amount of milk had the effect to maintain normal growth, which otherwise soon ceased. The effect was shown not to be due to greater amount, energy value or palatability of the ration containing the small amount of milk. The nature of the important principle was not determined.

One of us (E. B. F.) has had similar experience in feeding experiments with pigs on a basal ration of pearl hominy, wheat gluten, blood albumen and corn bran, to which were added various pure phosphorus compounds. It has often been the case, with rations other than those containing glycerophosphates, that in order to keep the pigs alive until the end of the experiment it has been

necessary to introduce a small amount of corn into the ration. The improvement was always marked. At these times we were unable to get the pigs into good condition by the addition to the ration of corn oil, mangel wurzels, potassium citrate, calcium carbonate or soda.

Osborne and Mendel (1911a) in their first year's investigation on feeding with isolated food substances (reported in Carnegie Institution Publication 156, Part I) conducted many experiments in the feeding of white rats on rations of pure casein, cane sugar, starch, lard, agar and inorganic salts. Varying results, as determined by the salt mixtures, were obtained. Weight was maintained and nitrogen stored over considerable periods of time with both young and mature rats, but without significant gain in weight, on rations containing but a single protein. One animal was maintained for 217 days on a diet in which the sole protein was glutenin.

In the second year's work, as reported in Part II of the above-mentioned publication, a large number of pure proteins were compared, some containing phosphorus, and others free from this element. A noteworthy change of method was the addition to the ration of "protein-free" milk, a preparation made from skim milk by precipitation of the casein with hydrochloric acid, filtration, and evaporation of the whey.

Active growth was obtained with casein, ovalbumin, lactalbumin, edestin, glutenin and glycinin, each as the sole protein constituent of the ration. With gliadin, and hordein there was little or no growth, and with zein weight was not maintained. The use of protein-free milk rendered this series of experiments the first thoroughly successful attempt to induce growth in rats with such isolated food substances. The maximum normal size of the animals was not attained, however, as the authors state in their later work on fat-free foods (Osborne and Mendel, 1912b), but an increase to several times the initial weight was produced on rations at least essentially free from purins and from organic phosphorus compounds. See also Osborne and Mendel, 1911b.

In the article entitled "Ueber Fütterungsversuche mit isolierten Nahrungssubstanzen" (1912b) Osborne and Mendel review their previous work and add reports of further similar tests of the ability of rats to gain in weight on rations in which certain legume and other proteins constituted the sole source of protein nutriment. A table is presented in which the many pure proteins tested are arranged in the order of the gain in weight induced by them, in rats, during 30 days. In the order named, beginning with those which cause loss in weight they are as follows: Phaseolin, zein, gelatin and conglutin, the loss in weight of the last-mentioned being

least. Then in a series of ascending efficiency are mentioned rye gliadin, hordein, pea legumin, wheat gliadin, vignin, legumelin, hemp-seed glutelin, edestin, glycinin, wheat glutenin, cotton-seed globulin, lactalbumin, maize glutelin, excelsin, squash-seed globulin, ovalbumin, casein, and, most efficient of all, ovovitellin.

In a paper on "The Rôle of Gliadin in Nutrition" Osborne and Mendel (1912c) showed that the gliadins of wheat and rye, as well as the closely related hordein of barley, suffice for the maintenance of rats without growth. A female rat after 178 days with gliadin as its sole protein gave birth to four young. At the end of 30 days 3 were removed. The one remaining with the mother, however, failed to thrive on the gliadin food. The authors consider that in this experiment there must have been a synthesis of those protein "building stones" which were lacking in the intake during the period of gestation and lactation. The rat only maintained its weight previous to mating. During pregnancy the gain in weight was very rapid. Subsequent to pregnancy, however, the loss in weight was pronounced, and the rat died 94 days after bearing young, her weight at that time being only a little more than half that at the time she was mated. No post-mortem was held.

A number of charts are presented showing the history of experimental animals subsequent to the period of normal growth on the rations containing but a single protein. After such normal increase in weight, as previously mentioned, these animals reached a period of rapid decline in weight. Body analyses, to demonstrate that the normal increase in weight was in every way normal in character, would be of interest in this connection.

In "Maintenance Experiments With Isolated Proteins" these authors state that "every animal has sooner or later declined when fed with mixtures of isolated and purified proteins, carbohydrates and fats together with inorganic matter in the form of crystallized salts. In nearly every case the decline has been sudden, with strong evidence that death would soon have ensued had not the food been changed. In each case immediate recovery has followed a change in the diet, thus showing the experimental foods to be inadequate for prolonged nutrition." They state, however, that "with the aid of 'protein-free' milk it is possible to maintain rats for periods equal to practically their entire adult lives on foods containing a single purified protein." They also note the work of Hopkins (1912) who shows that milk, as well as other natural food materials, contains unknown substances which, even in very small quantities, suffice to induce normal and continued growth, for several weeks, at least, in rats maintained on artificial mixtures of food substances which are otherwise inadequate for growth.

Twelve rats were maintained more than 400 days, and 5 rats more than 500 days on rations of isolated foodstuffs free from more than the merest possible traces of purins and of phosphoproteins.

In 1912 Osborne and Mendel published a series of four papers all bearing on the subject of protein synthesis, and incidentally on the synthesis of compounds of phosphorus. The method of experimentation was modified by the use of an artificial mixture of inorganic salts and milk sugar in imitation of the protein-free milk preparation which had made possible the success of the work of the previous year. This artificial preparation proved to be the most efficient salt mixture thus far compounded. In their work on "Feeding Experiments With Fat-Free Food Mixtures" (1912a) they were successful in causing growth of young white rats on rations of isolated food substances which were entirely free from fat, and at least essentially free from any compounds of lipoid nature, the protein being present in two cases as casein, in another as casein and edestin, and in another as edestin alone. Phosphorus was present in the last-mentioned only in the authors' "artificial protein-free milk." In this last case the curve of growth shows that the rat increased in weight to five times the initial weight in 60 days. It is difficult to believe that any sort of redistribution of constituents could make possible so considerable an increase in body weight without extensive synthesis of all of the phosphorus-containing compounds necessary to growth. The actual proof of such synthesis by body analysis of the experimental subjects will doubtless be forthcoming at an early date. That the growth was normal in composition was not in any way proven.

These authors were unable, however, similarly to induce growth in mice on these rations, and they note the agreement of their experience in this matter with that of Stepp.

Osborne and Mendel (1913) once more report their failure even to maintain mature animals indefinitely on artificial foods and inorganic salts. They write as follows (p. 132), "It is true that in several instances we have succeeded in keeping grown rats in health and in apparent nutritive equilibrium on purely artificial food mixtures over periods far longer than the experience of our predecessors had led us to expect. But the outcome has never been satisfactory in the sense of extending over what may be considered as the larger portion of the life-span of an adult animal. Successful maintenance has been secured only when the animals have been fed, in part at least, with foods containing our 'protein-free milk,'..... The superiority of the latter foods, compared with any purely artificial

food mixture in repairing the depleted body weight of animals that have begun to decline on the artificial salt mixtures tested is beyond question."

But even with the use of this "protein-free milk" growth may not be sustained in rats in a normal manner, "a few stopping after sixty days of growth, others continuing to grow for 100 days or more. After normal growth stops, the animals may remain in constant weight for a few days, or grow very slowly, and then suddenly decline and die unless a change is made in the diet. ..... The conclusion seems inevitable, therefore, that the 'protein-free milk foods' are deficient in, or completely lack, something which milk contains and which is indispensable for perfect growth."

The importance of certain inorganic elements not usually considered in nutrition investigations, namely iodine, manganese, fluorine and aluminium, was demonstrated by the addition of very small amounts of salts of these elements to the artificial protein-free milk previously mentioned. Much better results in feeding experiments were obtained with these elements present than in their absence, and a considerable portion of the favorable results obtained with the previous use of artificial protein-free milk must be considered to have been dependent on inorganic impurities present in the chemicals used in its preparation.

The authors show that butter contains the principle which is present in milk, lacking in their "protein-free milk," and which is essential to normal growth.

Hopkins and Neville (1912) also fed a large number of rats on the diet used by Osborne and Mendel, but the rats ceased to grow before the attainment of full normal size.

Ruth Wheeler (1913) maintained white mice in health for 6 months on an artificial diet containing but a single protein (casein).

Stepp (1913a) experimented on mice, with various lipoid-free diets, plus lipoids of diverse sorts and conditions. The lipoids of brain, egg yolk, etc., possessed life-saving power under certain conditions, but this capacity is lost through heating. Stepp speculates as to the probability of the essential nutrient being lecithin. Commercial lecithin, however, had not the life-saving power, perhaps because of modification in the course of separation from the natural product containing it, perhaps because another phosphatid is required.

Stepp (1913b) has studied the importance to animal life of the lipoids, phosphorized and otherwise, as separated from foods by various solvents. Experimenting with mice—ether seems not to remove essential nutrients from foodstuffs; alcohol extraction, however, leaves the food incapable of sustaining life.

Acetone extract of egg yolk does not contain the essential nutrients removed by alcohol, nor does an alcohol extract of the acetone extraction residue. Thus it appears that acetone removes a part, but not all, of the essential nutrients of egg yolk which are soluble in alcohol. A mixture of lecithin, cholesterol, cephalin, cerebron and phytin can not compensate for the substances extracted from the diet by alcohol-ether.

McCollum and Davis (1913a) obtained normal gain in weight of rats during 75-100 days on a ration of casein, dextrin, agar-agar and inorganic salt mixtures similar to the mineral content of eggs or milk. Such mixtures, however, do not support growth indefinitely. In a later paper (1913b) these authors state that beyond 100-120 days little or no increase in weight can be produced on such rations as the above. That animals fed on these rations of purified food substances are in a physiological state which is nearly normal was concluded from the fact that three female rats produced young after being fed only casein, carbohydrates, lard and salt mixtures for periods of 108, 127 and 142 days, respectively. These rats had made approximately normal growth for about 80 days on this ration. In none of these cases, however, were the mothers able normally to nourish the young. The authors believe that cessation of growth on such rations as the above is due to the animals' "running out" of some essential organic complex, which they determine to be present in the ether-extract of egg and of butter. Lard and olive oil were not similarly efficacious. The feeding of lecithin and cholesterin gave results which the authors characterize as "very doubtful." The data were not presented.

In applying to human nutrition and to live-stock feeding the results of these experiments with rats and mice, it is our feeling that, in spite of the fundamental similarity of the nutritive processes of all vertebrates, we should consider the possibility of important differences in the metabolism of remotely related forms.

In the literature on this subject we note a marked tendency on the part of some whose experience with animals has been confined to laboratory work with a very few species, to ascribe to animals generally, without qualification, the physiological capacities of each species. Many important differences are known to exist in the metabolism of vertebrates. As a single instance of this—some mice can live without drinking. While consuming only air-dry foods the metabolic water produced by oxidation within the tissues is adequate for the performance of all necessary functions. Such a fact should convince us of the need of conservatism in the practi-

cal application of some of our experimental results before they have been shown actually to possess significance in relation to the animal and the conditions of interest.

SUMMARY ON NUTRITIVE VALUES OF ORGANIC AND INORGANIC PHOSPHORUS

In the light of our present understanding, we must deplore the imperfect and inconclusive character of much of the work on this subject. That the evidence is not more satisfactory is because it has been only with the gradual accumulation of knowledge in this field that investigators have come to realize the difficulties and the requirements of a positive solution of this problem.

Considering the evidence as a whole, however, there is much of value, and even the more imperfect work, in the aggregate, produces a composite impression which can hardly fail to affect opinion; and that this should be true is perfectly proper, unless there be, throughout the work, a neglect of absolutely essential considerations. Candor requires that we admit one such possibility. In many experiments, at least, there has been no guarantee of the purity of the organic compounds used, and no particular effort to guard against the influence of other useful compounds associated with the organic phosphorus in the natural products and also in the isolated compounds as used in these investigations.

This consideration we must bear in mind. It does not invalidate all of the work on this subject, but should serve to increase the scientific conservatism with which we naturally regard the evidence. Considering that we have sufficiently qualified our conclusions we shall point out the apparent significance of the foregoing investigations.

One point, at least, in this connection, we may regard as definitely established. Considering the phosphorus requirement as a whole, an amount of organic phosphorus equal to a very small part of the total is sufficient for growth and reproduction, provided inorganic phosphorus be present in sufficient amount. This fact is not likely to be questioned, in consideration of the very small proportion of the total phosphorus of the animal which is present in organic combination.

That organic phosphorus is absolutely essential to any animal has not been demonstrated. The proof that inorganic phosphorus can serve all of the purposes for which any animal needs phosphorus is incomplete. There is much evidence to imply that with some species, at least, some organic phosphorus compounds are more useful than is inorganic phosphorus in the sense of being more readily and economically utilized, and of maintaining a higher state

of vitality as revealed by tissue enzyme estimations, the difference probably depending, in part at least, on the fact of the partial absorption and utilization of organic phosphorus compounds as such, without complete digestive cleavage.

An important aspect of this problem is afforded by the results of feeding experiments on rats and mice, with simple purified nutrients, and by the results of investigations of the cause of beriberi (see Beriberi). In the light of these studies the synthesis of organic phosphorus compounds in a normal manner seems to be dependent on the presence of minute quantities of certain unknown compounds which are found in natural foodstuffs, and which act like enzymes, catalyzers or activators. Such essential compounds are found in milk and in eggs and other natural foods of both plant and animal origin. Lack of such nutrient principles in white rice and patent flour has been shown to be the cause of beriberi, and Funk suggests that a deficiency of the food in these unknown compounds, for which he proposes the name "vitamines," produces a predisposition to many other diseases such as polyneuritis in fowls, epidemic dropsy, experimental scurvy in animals, infantile scurvy, ship beriberi and pellagra. From the facts of the occurrence of these substances in rice polish, and their absence from polished rice; and also their presence in whole wheat flour, and absence from white flour, we must conclude that in vegetable foods their distribution is localized in certain tissues.

It therefore seems not at all unlikely that the many demonstrations of superior nutritive value of organic to inorganic phosphorus compounds have been influenced by other beneficial substances occurring in association with them in natural foods, and contained as impurities in these organic phosphorus compounds as isolated and used in nutrition investigations. As to the relative importance of this factor and others we are as yet unprepared to make positive assertions; but these recent studies at least raise the question as to whether the apparent superiority of organic to inorganic phosphorus compounds is due to these organic compounds by themselves, or whether their superiority is dependent on minute quantities of certain associated compounds. However this question may be settled, these studies certainly suggest that, if the natural organic phosphorus compounds are not of superior usefulness, or are not essential to the maintenance of growth in animals, then other nutrients associated with them in the natural foods *are* essential, and the result, therefore, is to put a new emphasis on the value of the natural organic foodstuffs as compared with inorganic or artificially synthesized nutrients and certain manufactured foods.

SOME COMMON FOODS IN RELATION TO PHOSPHORUS METABOLISM

MISCELLANEOUS EXPERIMENTS WITH MEN AND ANIMALS

The relative capacities of common foods to supply the phosphorus requirements of animals is a subject of much practical importance on which we have comparatively little evidence, and, in view of the fact that the comparisons must be made, if they are to be of practical value, not between individual foodstuffs, but between mixed rations, wholly satisfactory evidence in this field is not to be expected. However, very imperfect evidence is not necessarily without value, and is often the only sort obtainable with reference to our most important problems.

EXPERIMENTS WITH HUMAN BEINGS

Surmont and Dehon (1903) conducted 24-hour balance experiments with human subjects in the comparison of white bread and whole wheat bread, eaten with distilled water only. A portion of the results are as follows:

NITROGEN AND PHOSPHORUS BALANCES COMPARING WHOLE WHEAT BREAD WITH WHITE BREAD, WITH TWO HUMAN SUBJECTS IN TWENTY-FOUR HOUR EXPERIMENTS—Grams

Kind of bread	Bread eaten	Nitrogen				Phosphorus (P_2O_5)			
		Food	Urine	Feces	Balance	Food	Urine	Feces	Balance
White.....	680	8.357	7.089	1.573	−0.305	1.455	1.859	0.930	−1.334
Whole wheat.	605	11.942	11.445	2.485	−0.988(1)	6.419	5.265	2.683	−1.529
White.....	950	11.941	12.130	3.835	−4.024	1.990	1.517	1.118	−0.645
Whole wheat.	950	18.230	12.440	7.021	−1.231	9.471	6.422	3.657	−0.608

(1) Should be —1.988 to correspond with other data.

The authors state that the two lots of white bread contained 1.229 percent and 1.257 percent nitrogen, and 0.214 and 0.199 percent P_2O_5; the whole wheat bread 1.974 and 1.919 percent nitrogen, and 1.061 and 0.997 percent P_2O_5.

A larger proportion of the phosphorus of the white bread was found in the feces than of the whole wheat bread. The apparent digestibility of the nitrogen was about the same in both cases. The periods, however, were so short that the results have only corroborative value. The very considerable phosphorus deficit on the whole wheat bread diet, with an intake of 6.4 gm. P_2O_5 in one case and 9.47 gm. in another is remarkable, since these amounts of phosphorus are much more than enough to maintain phosphorus equilibrium under ordinary conditions. The very short periods give results indicating habit of phosphorus metabolism rather than phosphorus requirements.

Surmont and Dehon (1904) continued their study of white and whole wheat bread at a later date. A part of their figures are as follows:

AVERAGE DAILY NITROGEN AND PHOSPHORUS BALANCES WITH TWO MEN COMPARING WHITE BREAD WITH WHOLE WHEAT BREAD IN THREE-DAY PERIODS—Grams

Kind of bread	Nitrogen				Phosphorus (P_2O_5)			
	Food	Urine	Feces	Balance	Food	Urine	Feces	Balance
White	12.213	10.377	2.458	−0.622	6.384	4.004	2.311	+0.069
Whole wheat	11.718	10.227	2.566	−1.076	8.163	5.081	2.887	+0.195
White	12.213	12.034	2.414	−2.235	6.384	4.082	2.238	+0.066
Whole wheat	11.718	11.976	2.527	−2.785	8.163	5.125	2.870	+0.168

The subjects were first brought to nitrogen equilibrium on a constant mixed diet; then followed the 3-day experiments on whole wheat bread as a part of the mixed diet. Nitrogen equilibrium was again established in an intermediate period, and then followed the period in which white bread was consumed with a mixed diet.

The authors concluded that the phosphorus of whole wheat bread is as well absorbed as that of white bread, and that the coëfficient of retention of the phosphorus of whole wheat bread is higher than that of the phosphorus of white bread. The assimilation of the nitrogen of the whole wheat bread was found somewhat lower than with the white bread.

Newman, Robinson, Halnan and Neville (1912) compared white and whole wheat breads in digestion experiments of 7 days' duration with four men. The phosphorus of the whole wheat bread, being present in much greater quantity than in the white bread, was apparently absorbed as efficiently, and therefore in larger proportion to absorbed nitrogen, thus approaching the ratio of these constituents as absorbed from efficient mixed dietaries. The nitrogen of the white bread was considered to be absorbed 3.5 percent more efficiently than that from the whole wheat bread.

Schlossmann and Moro (1904) attempted to compare metabolism of a 28-year-old man on a diet of cow's milk with the same on a diet of human milk, but psychic factors rendered results pathological on the latter diet, and the figures therefore have no especial value. In a 2-day period on cow's milk, cream, milk sugar and cognac, with a daily intake of 4.487 gm. CaO and 6.113 gm. P_2O_5, there was a storage of 1.60 gm. CaO and 1.33 gm. P_2O_5. The subject weighed 59.1 kg.

Wiley, and associates (1904, 1906, 1907, 1908a,b) studied metabolism in healthy young men as influenced by various food preservatives. Their results on phosphorus metabolism were rather variable, and were not striking.

From the administration of 3 gm. boric acid, or equivalent amounts of borax daily, it would appear that this preservative slightly decreases phosphorus retention.

Salicylic acid and salicylates in quantities of 0.210 gm.—2.00 gm. per day appeared to increase to a slight extent the absorption of phosphorus from the intestine, and to lead to its retention in the body. The positive phosphorus balance was somewhat greater in amount during the preservative period than either before or after.

Sulphurous acid and sulphites in quantities of 0.171 gm. to 1.020 gm. (SO_2) per day increased the feces phosphorus. The authors assume that this increase is due to inhibited absorption from the intestine.

Benzoic acid and sodium benzoate in quantities of 1.0—2.5 gm. daily of benzoic acid, or equivalent amounts of sodium benzoate, also caused a slight increase in feces phosphorus; while formaldehyde in quantities of 100-200 mg. daily caused a slight increase in phosphorus excretion, with a considerable deflection of phosphorus from feces to urine.

The experimental periods were of considerable duration and the scope of the work extensive. The feces were not marked at the beginning and end of periods.

Slowtzoff (1909a, 1909b) reports a comparison of calcium, magnesium and phosphorus metabolism on a diet containing meat with the same after the substitution of fish for meat. The experiment covered two periods of four days each. Under the influence of the fish the phosphorus and magnesium retention was increased, while the calcium retention was decreased. The author considers especially characteristic the increase of the calcium (about 60 percent) and magnesium (about 44 percent) of the urine above the amount present during the meat period. Of this article we have seen abstracts only.

The most important demonstration of specific effects of common foods on phosphorus metabolism is certainly the recent discovery of the cause of beriberi. In this disease profound disorganization of the nervous system is due to the lack of certain important activating principles in polished rice. For a discussion of this matter see Beriberi.

EXPERIMENTS WITH DOMESTIC ANIMALS

Verdeil (1849) analyzed the blood ash of different species of animals, and of dogs on various rations. He concluded that a difference of feed shows quickly in the composition of the blood, and that in the blood of animals eating meat, bread or grains alkali phosphates are abundant, and carbonates almost lacking, while with herbivora the opposite relation holds.

Landsteiner (1892) found no significant differences in the blood ash of rabbits fed on milk, and those fed on hay for 3½ months.

According to Hart, McCollum and Fuller (1909), the blood of four pigs that had received different amounts and kinds of phosphorus compounds in the diet showed a phosphorus range from 0.24 to 0.33 percent P (aver. 0.29 percent) of the air-dry matter. The calcium ranged from 0.026 to 0.038 percent Ca, with an average of 0.033 percent.

In the work of E. B. Forbes and associates (1914) the minerals (including phosphorus) of the blood were found to vary, in marked and consistent ways in accord with the character of the food. Ash varied between 0.90 and 1.04 percent, phosphorus between 0.38 and 0.64 percent, inorganic phosphorus between 0.009 and 0.019 percent, calcium between 0.0061 and 0.0085 percent, magnesium between 0.0034 and 0.0059 percent, potassium between 0.172 and 0.230 percent, sodium between 0.19 and 0.29 percent, sulphur between 0.120 and 0.166 percent and chlorine between 0.24 and 0.27 percent.

Alquier (1905-6), from feeding experiments on horses, concluded that beet molasses would increase the solubility, and therefore the assimilability, of the phosphorus of the ration, through the action of the considerable amounts of sodium and potassium present in this food. On the assumption that the greatly increased amounts of sodium and potassium introduced into the ration by the molasses replaced, in a measure, the calcium of calcium phosphate, it seems quite possible that the suggestion is in accord with the facts.

E. B. Forbes (1909) studied, in three experiments involving 120 pigs, the specific effects of a number of common foodstuffs, especially corn (maize), on the bodies of pigs, largely as to relations of fat, water and phosphorus. Results were obtained from the gain in live weight, and in weight of parts and organs, analyses of the tenderloin (*psoas magnus*) muscles, livers, kidneys, and cross sections of the body at the 6th rib, and also of the foodstuffs used. The first experiment involved 65 pigs in 13 lots of 5 each. The feeding lasted 60 days, and the pigs in the several lots gained in

weight from one pound to 1.7 pounds per head and day. This experiment was conducted in two series of 6 lots, one receiving food *ad libitum,* and the other receiving restricted amounts of the same foods, one lot being killed as a control at the beginning of the experiment. Two lots (one in each series) received corn alone, and of the remaining ten lots, two each received corn supplemented by linseed oil meal, wheat middlings, corn germ oil meal, soy beans and digester tankage.

The muscular increase was generally in the order of the phosphorus content of the rations, except with the lots which received tankage, the phosphorus of which was present mostly as bone.

The gain of fat and muscle were reciprocal; that is, arranging the lots according to gain in fat arranged them inversely as the gain in muscle. These facts suggest that common foods do not contain as much phosphorus as is essential to maximum growth of muscular tissue and skeleton. Lecithin phosphorus seemed not to be the dominant factor in this consideration.

Corn, which is characterized by low protein, calcium and phosphorus contents, in comparison with better-balanced rations, produced under-sized, over-fat animals, with small viscera, and deficient muscular development, and bones which lacked in size, strength and ash per unit of volume. The muscles were characterized by low protein and low ash content, and high content of fat, while the water in the tissue as a whole was low, but in the fat-free meat was high. These effects are due especially to lack of protein and of calcium, which seem to limit the usefulness of the phosphorus.

The second and third experiments involved 55 animals in 12 lots, commonly of 5 each. They were conducted in the same general way as the first, but the rations were composed of pearl hominy and blood flour to which were added certain phosphorus-containing preparations of interest. These were (1) water extract of wheat bran, containing an abundance of inosite-phosphoric acid, (2) bone flour, (3) lecithin and (4) sodium phosphate. The same amount of phosphorus was fed in disodium phosphate as in lecithin. In these later experiments studies were also made on the growth and composition of the bones (humeri). For numerical data see tables on pages 371 to 374.

The water extract of wheat bran appeared to contribute to the muscle-producing capacity of the ration, and bone flour was decidedly less useful in this way.

Marked characteristics of the muscular tissue produced in these experiments were the low phosphorus content (0.195-0.252 percent) of the muscle produced by rations containing the bran extract, and

the very high phosphorus content (0.352 percent) of the muscle produced by the ration containing lecithin.

In Experiment II the bones of the pigs which had received bone meal exceeded all others in volume, total ash, ash per c.c. of volume, and breaking strength. Clearly the bone meal was of direct value as a source of nutriment. Observation determined the fact that the deposit of bone salts was largely at the inside of the walls of the bones. In some cases this interior thickening of the walls proceeded almost to the obliteration of the marrow space. Certainly there is a much less definite upper limit for the mineral content of the bones than for other tissues. This is in harmony with their prominent storage function for mineral nutriment.

FOODS AND MINERAL NUTRIENTS CONSUMED (Forbes, 1909)

EXPERIMENT II

Lot	Rations Grams	Calcium Grams	Magnesium Grams	Potassium Grams	Sodium Grams	Sulphur Grams	Phosphorus Grams	Chlorine Grams	Excess normal acid C. C.
1	Corn 2114.2	.199	2.326	5.920	.973	2.981	6.237	.846	217.90
2	Hominy 1991.8 Blood-flour 165.6 Bran-extract, (larger amt.) 2039.4	1.092	3.500	7.239	1.358	4.236	6.641	1.491	149.11
3	Hominy 2068.9 Blood-flour 187.3 Lecithin 4.00	.822	.504	2.166	.921	3.728	1.562	1.518	198.50
4	Hominy 2074.3 Blood-flour 181.4 Bran-extract, (smaller amt.) 779.3	.936	1.675	4.140	1.100	3.980	3.429	1.531	176.50
5	Hominy 1821.2 Blood-flour 162.4 Bone-meal 20.9	5.747	.552	1.920	.915	3.286	3.610	1.337	54.91
6	Hominy 2068.4 Blood-flour 187.3 Sodium phosphate 1.8	.822	.504	2.166	1.152	3.728	1.562	1.518	188.48

EXPERIMENT III

1	Corn 1426.9	.134	1.571	3.998	.657	2.013	4.212	.571	147.14
3	Hominy 1548.6 Blood-flour 171.9 Bran-extract 589.7	.842	1.272	3.144	.958	3.214	2.655	1.245	138.63
4	Hominy 1570.4 Blood-flour 174.6 Bone-flour 11.0	3.406	.463	1.684	.879	3.054	2.390	1.247	90.86
5	Hominy 1286.9 Blood-flour 143.3	.616	.332	1.378	.672	2.500	0.934	1.021	122.70

In Experiment III the pigs were younger than in Experiment II, and could be persuaded to eat but a very small amount of the bone meal, the pigs on the ration of corn alone receiving more phosphorus than the lot on the basal ration plus bone meal. The bone data from this experiment, therefore, were less significant.

The pigs receiving the maximum amount of bran extract that they would tolerate, and receiving in this ration nearly twice as much phosphorus as another lot which was fed less of the extract, had smaller muscles and also smaller bones, the bones containing slightly less ash per cubic centimeter of volume, and the muscles less phosphorus than in the lot which received less of this supplement. The bran extract apparently contained some constituent which, when present in excess, tended to restrict the utilization of the phosphorus of the ration. This extract was very rich in magnesium.

ANALYSES OF TENDERLOIN MUSCLES (Forbes, 1909)—Percent

EXPERIMENT II

Lot	Rations	Water	Protein	Fat	Ash	Phosphorus	Proportion of phosphorus to protein	Phosphorus in ash
1	Corn	73.51	19.73	5.17	1.09	.264	1.34	24.22
2	Hominy; blood-flour; bran-extract, (larger amount)	73.62	18.85	5.17	1.13	.195	1.04	17.35
3	Hominy; blood-flour; lecithin	74.63	15.78	4.27	1.10	.352	2.23	32.00
4	Hominy; blood flour; bran-extract, (smaller amount)	72.74	20.67	4.22	1.21	.252	1.22	20.83
5	Hominy; blood-flour; bone-meal	72.83	20.13	5.12	1.08	.233	1.16	21.57
6	Hominy; blood-flour; sodium phosphate	72.87	20.74	5.14	1.10	.264	1.27	24.00
7	Check lot	73.57	18.53	4.97	1.10	.247	1.33	22.45
	EXPERIMENT III							
1	Corn	73.39	17.68	6.16	1.07	.228	1.29	21.31
2	Check lot	76.35	19.42	3.04	1.13	.238	1.23	21.06
3	Hominy; blood-flour; bran-extract	73.74	21.85	3.90	1.03	.195	.81	18.93
4	Hominy; blood-flour; bone-flour	73.20	18.30	4.46	1.12	.222	1.21	19.82
5	Hominy; blood-flour	72.81	20.39	4.52	1.15	.228	1.12	19.83

This series of experiments demonstrates a susceptibility of the animal body to change of composition as a result of the character of the food which is often underestimated and still more frequently denied. As an instance of this fact the above and the following tables are submitted.

From these tables we note that the phosphorus in muscle varied in amount, expressed as percent of protein, from 1.04 to 2.23 percent, and expressed as percent of ash, from 17.35 to 32 percent. In liver the phosphorus varied between 1.57 and 2.10 percent of the protein, and between 24.18 and 28.23 percent of the ash.

In the kidneys, the phosphorus varied between 1.32 and 1.99 percent of the protein, and between 18.47 and 27.90 percent of the ash.

These variations in gross proximate analysis are certainly sufficient to indicate profound changes in functional efficiency. Enzyme estimations in connection with such studies would probably be of value.

ANALYSES OF LIVERS (Forbes, 1909)—Percent

EXPERIMENT II

Lots	Rations	Water	Protein	Fat	Ash	Phosphorus	Proportion of phosphorus to protein	Phosphorus in ash
1	Corn	74.24	18.83	2.81	1.27	.320	1.70	25.20
2	Hominy; blood-flour; bran-extract, (larger amount)	73.52	17.19	2.46	1.37	.356	2.07	26.00
3	Hominy; blood-flour; lecithin	71.98	18.72	2.90	1.29	.364	1.94	28.22
4	Hominy; blood-flour; bran-extract, (smaller amount)	71.96	20.13	3.01	1.32	.364	1.81	27.58
5	Hominy; blood-flour; bone-meal	71.81	19.45	2.65	1.39	.361	1.85	25.97
6	Hominy; blood-flour; sodium phosphate	72.05	20.58	2.85	1.34	.324	1.57	24.18
7	Check lot	71.48	14.61	1.84	1.17	.291	1.99	24.87
	EXPERIMENT III							
1	Corn	70.77	16.08	2.32	1.21	.338	2.10	27.93
2	Check lot	71.21	18.12	3.01	1.33	.338	1.87	25.41
3	Hominy; blood-flour; bran-extract	71.65	20.44	2.49	1.30	.367	1.80	28.23
4	Hominy; blood-flour; bone-flour	70.43	19.31	2.03	1.30	.366	1.90	28.15
5	Hominy; blood-flour	70.64	20.97	2.26	1.34	.346	1.65	25.82

See also the tables on the following page.

Schkarin (1910) studied the influence of the diet of mother dogs on the development of suckling pups. No characteristic effects were observable of the diets of (1) vegetable food, (2) meat and milk, and (3) eggs and milk. The reason for negative results lies in the impossibility of modifying the composition of the milk, to any considerable extent, through the character of the food.

Fingerling (1911a) attempted to solve the question of the better utilization by ruminants of the phosphorus compounds of cereals and mill feeds than of roughage. After various tests, which threw no light on the matter, he fed, in comparison, fresh grass and hay

ANALYSES OF KIDNEYS (Forbes, 1909)—Percent

EXPERIMENT II

Lots	Rations	Water	Protein	Fat	Ash	Phosphorus	Proportion of phosphorus to protein	Phosphorus in ash
1	Corn	78.21	15.78	3.07	1.17	.232	1.47	19.83
2	Hominy; blood-flour; bran-extract, (larger amount)	80.68	14.34	2.65	1.02	.243	1.69	23.82
3	Hominy; blood-flour; lecithin	78.80	16.38	2.89	1.15	.258	1.58	22.43
4	Hominy; blood-flour; bran-extract, (smaller amount)	79.99	15.62	2.57	1.10	.250	1.60	22.73
5	Hominy; blood-flour; bone-meal	79.27	15.49	2.94	1.11	.205	1.32	18.47
6	Hominy; blood-flour; sodium phosphate	80.55	14.56	2.72	1.12	.234	1.61	20.90
7	Check lot	78.80	16.83	1.99	1.20	.262	1.57	21.83

EXPERIMENT III

1	Corn	76.70	17.07	4.95	1.14	.313	1.83	27.46
2	Check lot	80.32	14.37	2.11	1.12	.249	1.73	22.23
3	Hominy; blood-flour; bran-extract	79.78	15.79	3.41	1.11	.249	1.58	22.43
4	Hominy; blood-flour; bone-flour	77.18	16.01	3.92	1.14	.318	1.99	27.90
5	Hominy; blood-flour	77.84	17.00	3.91	1.07	.294	1.73	27.48

DATA CONCERNING DEVELOPMENT OF BONES (Forbes, 1909)

EXPERIMENT II

Lot	Rations	Volume of each humerus C. C.	Ash in each humerus Grams	Ash per c. c. Grams	Breaking strength Lbs.	Length Cm.	Longer transverse diameter Cm.	Shorter transverse diameter Cm.
1	Corn	108.0	32.92	.3048	509	13.88	2.25	1.63
2	Hominy; blood-flour; bran-extract, (larger amount)	111.8	33.33	.2981	575	13.68	2.23	1.67
3	Hominy; blood-flour; lecithin	118.0	38.97	.3303	736	13.70	2.20	1.66
4	Hominy; blood-flour; bran-extract, (smaller amount)	117.6	36.39	.3094	676	13.74	2.34	1.68
5	Hominy; blood-flour; bone-meal	121.3	46.22	.3811	791	14.00	2.28	1.71
6	Hominy; blood-flour; sodium phosphate	112.5	35.59	.3164	624	13.90	2.33	1.69

EXPERIMENT III

1	Corn	74.6	23.82	.319	502	13.1	1.83	1.37
2	Check lot	65.9	19.93	.3024	440	11.64	1.75	1.30
3	Hominy; blood-flour; bran-extract	100.1	28.01	.280	641	14.46	1.98	1.51
4	Hominy; blood-flour; bone-flour	94.4	28.97	.307	606	13.46	2.08	1.46
5	Hominy; blood-flour	93.7	20.56	.219	426	13.56	1.95	1.41

made from the same. Of the phosphorus of the hay 53.4 percent was used, while of the phosphorus of the fresh grass 91.0 percent was used. Fingerling, therefore, ascribes the difference in the value of the phosphorus in cereals and mill feeds, on the one hand, and roughages, on the other, to the resistance to digestion of the crude fiber of the latter, and its interference with the digestion of the phosphorus compounds.

We would suggest that the nature and amount of the bases present with the phosphorus in these two classes of foods should receive consideration in this connection. There is little calcium in the cereals and mill feeds, and much more in roughage.

Weiser (1911, 1912) has studied mineral metabolism with swine on cereal diets, with and without additional calcium. The balance data are as follows:

AVERAGE DAILY NITROGEN AND MINERAL BALANCES WITH SWINE ON RATIONS OF CEREAL FOODS WITH AND WITHOUT ADDITIONAL CALCIUM—Grams

Duration of period in days	Rations	Average body weight Kg.	P Food Urine Feces Balance	Ca Food Urine Feces Balance	Mg Food Urine Feces Balance	N Food Urine Feces Balance
21	1200 gm. corn	55.88	3.2073 1.0241 2.4841 −0.3009	0.2507 0.1428 1.3936 −1.2857	1.5868 0.1951 0.1206 +1.2711	21.39 15.38 3.19 +2.82
9	1000 gm. corn	53.37	2.6731 0.8134 2.2570 −0.3973	0.1996 0.1384 1.1298 −1.0686	1.3201 0.1337 0.1276 +1.0588	17.82 12.59 2.67 +2.66
8	800 gm. corn	44.12	2.1467 0.6663 1.1986 +0.2818	0.1559 0.0308 0.3206 −0.1955	1.0593 0.1623 0.3878 +0.5092	14.32 9.04 2.13 +3.15
	900 gm. barley; 160 gm. starch	52.55	2.5251 0.7950 1.2572 +0.4729	0.5621 0.0489 0.4934 +0.0198	1.1002 0.2718 0.7058 +0.1226	17.899 8.810 3.670 +5.419
10	1050 gm. corn; 5 gm. calcium carbonate	47.02	2.8167 0.2714 1.6960 +0.8493	2.1950 0.0766 1.2602 +0.8582	1.2528 0.2075 0.9440 +0.1012	18.78 12.08 2.36 + 4.34
7	900 gm. barley; 3 gm. calcium carbonate	49.93	2.5251 0.2862 1.2238 +1.0151	2.1961 0.0778 0.6699 +1.4484	1.1009 0.1962 0.5968 +0.3079	17.760 8.760 3.310 +5.690

Author's Summary. "1. By exclusive feeding on corn, growing swine experience a calcium and phosphorus deficit even when there is storage of flesh and fat. At the same time there is storage of magnesium.

"2. By the addition of calcium carbonate, not only was the calcium and phosphorus deficit relieved, but there was even a good retention of calcium and phosphorus. At the same time the storage of magnesium was decidedly lowered. The amount of calcium carbonate by which one may reckon on a good calcium retention is about 10-11 gm. per 100 kg. body weight.

"3. From what has been said it is evident that the bone requirement of young swine is not sufficiently met by a feed of only corn and barley, but this may easily be helped by adding calcium carbonate."

Hagemann (1912) obtained results in metabolism experiments with two wethers and a steer showing that calcium phosphate is more effective to increase nitrogen and calcium retention when finely milled with the feed than when simply mixed with the same at the time of feeding, a result in harmony with that of Herxheimer (1897), who found 18 gm. of calcium carbonate baked in bread more effective to increase the solvent power of the urine for uric acid than 30 gm. of the same fed as a powder. These results suggest that the mechanical relations of food constituents may affect their time and place of digestion, and, in this way, their final disposition. See also Landsteiner (1892); effects of hay and milk on blood-ash of rabbits.

E. B. Forbes and associates (1914) have shown, in their experiments of Series IV, that corn in the diet of swine has definite specific effects on various items of composition, among these,—the total and inorganic phosphorus of the blood, the lecithin content of the liver; and the composition of the ash of the bones.

Forbes, Beegle, Fritz and Mensching (1914) conducted an extensive mineral metabolism experiment with swine, phosphorus balances being included. Five barrow pigs, about 6 months old, and all from the same litter, were the subjects of the experiment.

Confined in metabolism crates they were taken through eight 10-day collection periods, separated by 7-day intervals on the next ration to follow, the change of food being made abruptly at the end of the collection period. The five animals were given the same kind of food, the results therefore being based on five repeats.

The foods used in the several periods were as follows:

1. Corn.
2. Corn; soy beans.
3. Corn; linseed oil meal.
4. Corn; wheat middlings.
5. Corn; meat meal.
6. Corn; skim milk.
7. Corn.
8. Rice polish; wheat bran

They were, therefore, the common practical foods for swine in this country, except for ration No. 8, composed of rice polish and wheat bran, these feeds being selected on account of their very high content of magnesium as compared with calcium. Corn was fed alone in the first and seventh periods to show any such changes as might be due to the long-continued routine or to increasing age.

The observations covered the usual proximate analyses of foodstuffs and feces, daily nitrogen, creatinin and ammonia estimations on the urine, also determinations of sodium, potassium, calcium, magnesium, sulphur, phosphorus and chlorine on foods, urines and feces; and further, a slaughter test on the five animals after the termination of the experiment.

The condensed mineral balance data are in the table on p. 378. These figures represent averages of results from five individuals. The uniformity of the results with the several individuals was sufficiently marked to warrant averaging.

The phosphorus balances in these experiments were all positive, except for one individual on the ration of corn alone. In no case, however, was there any considerable retention of phosphorus on corn alone. Except in one case the phosphorus retention in the several periods was in the same order as the intake. This exception was the ration containing the wheat middlings. The peculiarity of the phosphorus of this ration was a large proportion of triticonucleic acid, and the phosphorus of this ration was much less efficiently retained than the phosphorus of the rations containing meat meal and milk. With a much smaller intake of phosphorus in meat meal and in milk the retention was much greater. Two circumstances unfavorable to phosphorus retention in the wheat middlings ration were the presence of much less calcium and much more magnesium than in the meat meal and milk rations. The results were increase in both urine and feces phosphorus.

The magnesium of the food is shown to be a prominent factor in the partition of the phosphorus between urine and feces, an increased proportion of magnesium to phosphorus in the food increasing the proportion of feces to urine phosphorus. There was no such prominent effect of magnesium to restrict phosphorus retention.

During the feeding of skim milk there were lower proportions of potassium, magnesium, sulphur, chlorine and phosphorus in the feces than during any other period; and this period was also characterized by the maximum percentage retention of the calcium, magnesium, sulphur and phosphorus intake.

MINERAL METABOLISM OF SWINE ON RATIONS COMPOSED FROM COMMON FOODS

Forbes, Beegle, Fritz and Mensching (1913)

Average for Five Pigs—Grams

Period No.	Approximate live weight Kg.	Rations	K Food	K Urine	K Feces	K Balance	Na Food	Na Urine	Na Feces	Na Balance	Ca Food	Ca Urine	Ca Feces	Ca Balance	Mg Food	Mg Urine	Mg Feces	Mg Balance	S Food	S Urine	S Feces	S Balance	Cl Food	Cl Urine	Cl Feces	Cl Balance	P Food	P Urine	P Feces	P Balance	N Food	N Urine	N Feces	N Balance
II	52	Corn	1357.2	10.187			4.351				0.748				2.171				3.227				4.753				5.402				37.352			
		Soybeans	271 4	4.789			1.253				0.092				0.222				1.561				3.760				1.209				18.679			
		Salt	6.387	2.569			0.524				0.900				1.902				0.622				0.027				3.524				6.957			
		Water	3461			+2.828				+2.573				−0.243				+0.046				+1.044				+0.966				+0.669				+11.717
III	64	Corn	1590.4	9.168			4.101				1.380				3.363				3.759				5.739				6.581				41.352			
		Linseed oil meal	318.1	4.775			2.192				0.109				0.510				1.607				4.630				1.152				22.313			
		Salt	7.485	3.101			0.746				0.927				2.946				0.805				0.042				4.923				7.678			
		Water	5247			+1.292				+1.163				+0.344				−0.093				+1.346				+1.067				+0.507				+11.361
IV	71	Corn	1110.7	12.471			4.605				0.963				4.454				3.664				5.456				10.335				41.286			
		Wheat middlings	837.9	6.048			2.173				0.182				0.528				1.698				5.019				3.754				20.803			
		Salt	7.642	4.528			1.027				0.698				3.849				0.898				0.138				5.524				7.573			
		Water	5074			+1.895				+1.405				+0.083				+0.076				+1.068				+0.299				+1.058				+12.909
V	78	Corn	1705.3	6.916			6.090				5.233				2.151				3.631				9.601				7.344				40.420			
		Meat meal	170.5	4.167			5.310				0.211				0.341				1.163				8.725				2.125				22.671			
		Salt	7.356	1.572			1.061				1.740				1.911				1.024				0.035				3.504				9.741			
		Water	4768			+1.178				−0.281				+3.282				−0.101				+1.444				+0.841				+1.714				+8.007
VI	86	Corn	1688.2	10.121			4.588				4.628				2.368				3.747				8.148				7.763				41.925			
		Skim milk	3436.2	8.055			3.127				0.186				0.420				1.763				6.540				2.497				25.287			
		Salt	6.620	1.609			0.755				1.375				1.821				0.480				0.012				3.359				4.872			
		Water	2692			+0.456				+0.706				+3.047				+0.127				+1.503				+1.596				+1.906				+11.766
VII	94	Corn	1688.2	5.929			2.979				0.226				1.886				2.571				5.008				4.537				24.266			
		Salt	6.620	2.864			2.693				0.132				0.278				1.401				4.508				1.669				15.197			
		Water	5733	1.877			0.533				0.520				1.727				0.404				0.031				2.802				3.979			
				+1.188			−0.247				−0.427				−0.119				+0.766				+0.469				+0.065				+5.090			
VIII	97	Rice polish	1110.1	17.481			4.185				0.773				9.276				2.863				5.255				20.708				31.480			
		Wheat bran	370.1	15.062			1.243				0.110				0 436				1.002				3.709				0.863				15.858			
		Salt	5.803	4.215			1.074				1.161				9.580				0.812				0.058				14.923				6.578			
		Water	6292			−1.796				+1.868				−0.498				−0.741				+1.038				+1.489				+4.922				+9.044

Corn is shown to be more deficient in calcium than in any other nutrient; its magnesium content is also low, and its phosphorus content allows of but slight retention. At the same time the nitrogen retention is quite considerable. In spite of the slight retention of phosphorus its amount was considered as insufficient, since there was present hardly more than the amount required for maintenance, at a time of life which would naturally be characterized by extensive storage of phosphorus.

The results, in general, show that the mineral requirements of swine are apt not to be satisfied during cereal feeding. A dry-lot fattening process probably involves, as a rule, considerable draft upon mineral stores previously accumulated during periods of access to green feeds.

In a series of experiments by Forbes and associates (1914), with swine, three lots of pigs (5 in a lot), receiving corn in the ration, differed as a group from five other lots which received no corn in the ration, in several respects, as follows: Each of the three lots of pigs receiving corn had more potassium and magnesium, and more total and inorganic phosphorus in the blood, more magnesium and phosphorus, and less calcium in the bone ash, and more lecithin in the liver than any one of the five lots which had not received corn.

For a summary on common foods in relation to phosphorus metabolism see p. 395. See also the following sections on the phosphorus content of milk, and the phosphates of the bones, as affected by foods.

THE PHOSPHORUS CONTENT OF MILK AS AFFECTED BY FOODS

The idea of modifying the composition, and thus the nutritive value of milk, through the character of the food, is ancient, and has been the inspiration of many investigations. Some misconceptions among the conclusions reached have been due to the relatively considerable variations in the composition of the milk during the course of the period of lactation.

Among the earlier observations were those of Böcker (1849) who stated that administration of calcium phosphate to wet nurses whose milk was poor in lime served to enrich the milk in this constituent; and Ssubotin (1866), who studied the composition of dog's milk as affected by various rations, and ascribed an increased casein content to fat in the diet; also Decaisne (1871) who made observations on 43 lactating women during the siege of Paris. Hunger prevailed; the flow of milk was often insufficient to nourish the infants, and 12 died of starvation. The milk was low in casein, fat, sugar and salts, but high in albumin.

Weiske (1871b) studied the effects, on the composition of cow's milk, of adding 20 grams daily of acid calcium phosphate to a ration which the cows had been consuming regularly during a protracted period. There were no differences caused by the use of calcium phosphate, nor did Yvon (1879) succeed in increasing the phosphate of cow's milk in this way; but Hess and Schaffer (1891) claim that they did produce increased phosphorus in the milk ash. The average percent of P_2O_5 in the ash of the milk of three cows before feeding the phosphate was 25.80; after about a month this figure was increased to 27.52, and after about two months to 29.54; but it was not shown by the use of controls that the advance in the period of lactation did not enter into the production of this result. Sagnier (1891) reports that Charles Gravier, by special feeding (the nature of the feeding is not revealed), was able to furnish for the hospitals milk containing from 2.30 to 2.50 gms. phosphoric acid per liter. Duclaux (1893) concludes that milk which is sold as rich in phosphate, because of phosphate feeding, is found not to be so on analysis.

Hills's experiments (1887, 1894) with ground-bone feeding showed, first, that the added phosphorus did not all appear in the feces; then that it increased somewhat the phosphoric acid content of the milk of the cows; in one case from 0.2142 to 0.2263 percent, and in another from 0.1809 to 0.1909 percent.

J. Neumann (1893a) reports an experiment in which the addition of a calcium phosphate preparation to a feed already supplying sufficient quantities of the mineral constituents for milk production seemed to cause a slight rise in the lime and phosphoric acid content

LIME AND PHOSPHORIC ACID OF MILK AS AFFECTED BY CALCIUM PHOSPHATE ADDED TO THE FEED (J. Neumann, 1893a)

Date	Milk		In 1000 gm. milk		Percent of ash		In gms. per cow		
	Kg.	Ash Percent	Lime	Phosphoric acid	Lime	Phosphoric acid	Lime	Phosphoric acid	
Aug. 22	27.16	0.77	1.4950	1.9271	19.42	25.03	13.53	17.44	Without added phosphate; about 80 gm. lime, and 110 gm. phosphoric acid per day per cow
" 23	27.40	0.77	1.4804	1.9594	19.23	25.45	13.51	17.88	
" 24	28.20	0.77	1.4618	1.9930	18.98	25.88	13.74	18.73	
" 27	24.85	0.75	1.4355	1.8865	19.14	25.15	11.88	15.62	
" 31	25.79	0.75	1.4371	1.9307	19.16	25.74	12.36	16.61	
Sept. 3	25.67	0.78	1.5566	1.9864	19.96	25.47	13.32	17.00	40 gm. lime and 33 gm. phosphoric acid per day per cow added as calcium phosphate
" 7	25.00	0.78	1.4995	1.9868	19.22	25.47	12.49	16.55	
" 13	25.50	....	1.5252	1.9685	(19.81)	(25.56)	12.96	16.73	
" 20	24.30	0.77	1.5916	2.0262	20.67	26.31	12.90	16.41	
" 28	24.12	0.77	1.5509	2.1323	20.14	27.69	12.47	17.14	

of the milk, but only slight, and only after three or four weeks' duration of the phosphate feeding. The first effect of the phosphate was suddenly to reduce the milk flow. The milk of three cows was mixed for the analyses quoted on p. 380. The first addition of phosphate was made on the evening of August 24.

Sanson (1894) reports the following results, which were considered to show increasing amounts of phosphorus in milk, associated with increasing amounts of Na_2HPO_4 added to the feed, up to the dose of 22 gms., no further increase occurring with greater amounts of the phosphate. The increased phosphorus of the milk was all in the serum, the casein not showing any increase.

PHOSPHORUS OF MILK INCREASED BY PHOSPHATE FEEDING
Sanson (1894)

Day	Dose of sodium phosphate Grams	Density of milk	P_2O_5 of milk Grams per 1000	Increase of P_2O_5 Grams per 1000
1	0	1.032	1.438	0
2	10	1.031	1.984	0.546
3	12	1.033	2.046	0.608
4	14	1.031	1.946	0.508
5	16	1.029	2.046	0.608
6	18	1.032	2.084	0.646
7	20	1.032	2.145	0.707
8	22	1.036	2.170	0.732
9	24	1.034	2.070	0.632
10	26	1.037	2.108	0.670
11	28	1.034	2.083	0.645
12	30	1.033	2.170	0.732

In the experiments of Jordan, Hart and Patten (1906), with two cows, the removal of the phytin from the bran fed was without significant change on the phosphorus content of the milk.

EFFECTS OF THE INGESTION OF PHOSPHORUS COMPOUNDS ON THE COMPOSITION OF MILK—MEAN DAILY OUTPUT IN MILK
Jordan, Hart and Patten (1906)

Dates	Composition of milk, percent					Partition of phosphorus in milk				Ration
	Proteids	Casein	Fat	Sugar	Solids	Total Gms.	Nucleophosphorus Gms.	Soluble organic Gms.	Inorganic Gms.	
Mar. 12-Mar. 18	3.07	2.53	3.28	5.56	11.91	14.7	3.5	1.05	10.2	Oat straw, bran, rice meal, wheat gluten.
Mar. 30-Apr. 5	3.05	2.45	3.09	5.46	11.59	15.8	3.3	1.17	11.2	Oat straw, washed bran, rice meal, larger amount of gluten.
Apr. 24-May 1	3.22	2.66	3.73	5.47	12.41	....	...	....	....	
May 29-June 4	3.27	2.75	3.29	5.50	12.07	....	...	....	....	

Lipschitz (1906) notes that the feeding of bone meal reduces the milk flow, though increasing the total ash content of the milk.

Hart, McCollum and Humphrey's observations (1909) on one cow, extending over three and a half months, are summed up, so far as the ash of the milk is concerned, by saying: "Variations, within wide limits, in the form and quantity of supply of potassium, magnesium, or phosphorus did not influence the percentage content of these elements in the milk." It is to be noticed that the amounts yielded fell off markedly during the experiment.

Von Wendt's (1909) conclusion from his work was that neither the fodder nor the added salts exerted much influence on the composition of the milk, the phosphorus, casein and calcium being among the items least affected of all.

CHANGES OF AMOUNT AND COMPOSITION OF MILK ACCOMPANYING THE ADMINISTRATION OF CERTAIN SALTS (Von Wendt, 1909)

Cow or group	Dates	Supplements	Gain or loss in milk	Gain or loss of P_2O_5		Gain or loss of CaO	
			Grams	Percent	Grams	Percent	Grams
	Oct. 14-16	30 gm. potassium oxalate	−2000	−0.002	−2.3	−0.02	−4.8
	Oct. 20	60 gm. potassium oxalate	+900	0	+0.9	−0.03	−2.8
	Nov. 2-3	60 gm. potassium oxalate	−770	+0.006	+0.011	+0.006	+0.3
	Nov. 19-21	75 kg. beet leaves	−2150	+0.001	−2.1	0	−2.8
Cow 149	Dec. 16-18	30 gm. Ca HPO_4	+480	+0.002	+0.7	+0.042	+5.1
Cow 151	May 26-28	75 gm. Ca HPO_4	−300	−0.007	−1.1	+0.026	+2.9
Cow 150	May 26-28	75 gm. Ca HPO_4	−300	−0.003	−0.7	+0.024	+3.
Cow 150	Dec. 16-18	30 gm. Ca HPO_4	−600	+0.001	−0.7	+0.013	0
Cow 149	Dec. 25-27	90 gm. lime	+330	0	+0.35	−0.007	−0.25
Cow 150	Dec. 25-27	90 gm. lime	−400	−0.001	−0.23?	+0.021	+0.7
Cow 150	June 29-July 4	15 gm. lecithin	−1300	+0.004	−0.8	+0.020	+1.1
Gr. I	Apr. 22-24	30 gm. Ca HPO_4	+100	+0.002	+0.45	+0.007	+1.4
Gr. II	Apr. 22-24	30 gm. Ca HPO_4	−200	+0.001	−0.1	+0.006	+0.27
Gr. III	Dec. 7-9	90 gm. Ca HPO_4	+700	+0.001	+0.66	0.0	+0.63
Gr. II	Dec. 25-27	60 gm. Ca HPO_4	−220	−0.004	−0.2	−0.007	−1.0
Gr. III	Dec. 28-30	60 gm. Ca HPO_4	+400	+0.001	−0.06	+0.006	−1.0
Gr. I	Apr. 16-18	30 gm. lime	+1400	−0.001	+1	0	+2
Gr. II	Apr. 16-18	30 gm. lime	−500	−0.001	−0.57	−0.006	−1.18
Gr. I	Dec. 28-30	90 gm. lime	+400	+0.004	+0.9	+0.014	+2.3
Gr. II	Dec. 16-18	90 gm. lime	+40	+0.001	+0.2	+0.042	+5
Gr. III	Dec. 7-9	90 gm. lime	−110	+0.003	+0.15	+0.007	+0.5
Gr. II	Oct. 19-21	Beet leaves+Ca HPO_4	−460	−0.001	−0.6	0	−0.6
Gr. III	Oct. 19-21	Beet leaves+Ca HPO_4	−440	0	−0.4	0	−0.5
Gr. III	Nov. 29-Dec. 6	Beet leaves+Ca HPO_4	+900	+0.009	+2	+0.013	+2.2

Golding and Paine (1910) planned an experiment to test the possible effects on milk of pasturing cows on land manured with phosphates and potash, as compared with pasturing on unmanured land on grass of very poor quality. The ash, phosphoric acid, potash and lime of the milk (averaged) are the same for the two plots of land. The milk yield was considerably higher from the cows on the manured half, and its fat content higher from the other half.

According to the data furnished by Monvoisin (1910), both inflammation of the udder and tuberculosis affect the composition of the milk, lowering the percent of phosphorus in the ash. His data also show a distinct lowering of the casein content of milk in tuberculosis, both in absolute amount and in relation to total nitrogenous matter.

A. R. Rose and J. T. Cusick (1911) report inconclusive studies of the influence of phosphorus of the food on the yield and composition of goat milk.

Fingerling (1911b) studied the effects of diets rich and poor in calcium and phosphorus, and of dicalcium phosphate and calcium carbonate, on the yield and composition of the milk of goats; and also the effects of the same on the calcium and phosphorus balances. The balances responded quickly and consistently to variations in the intake of calcium and phosphorus. The effects of these conditions on the composition of the milk were slight; the effects on the amount of milk produced were more prominent.

INFLUENCE OF A LIME- AND PHOSPHORIC ACID-POOR DIET ON THE MILK SECRETION OF GOATS (Fingerling, 1911b)

Goat	Feed	Amount of milk	Ash	Percent of ash		No. of days
		Grams	Grams	CaO	P_2O_5	
A	Lime- and phosphoric acid-rich	1958	13.31	18.09	25.89	14
"	Lime- and phosphoric acid-poor	1886	13.30	18.04	25.80	14
"	Lime and phosphoric acid	1547	10.71	19.79	29.85	13
"	Lime and phosphoric acid	1388	8.90	21.44	30.41	13
"	Same with dicalcium phosphate	1493	10.35	19.97	28.35	14
"	Same with dicalcium phosphate and $CaCO_3$	1687	11.72	18.68	26.41	17
"	Like first period	1958	13.31	18.09	25.89	
31	Lime- and phosphoric acid-rich	1011	8.59	23.06	29.89	13
"	Lime- and phosphoric acid-poor	999	8.66	23.23	29.51	14
"	Lime- and phosphoric acid-poor	839	7.08	24.22	33.43	14
"	Lime- and phosphoric acid-rich	787	6.55	26.20	35.35	12
"	Lime- and phosphoric acid-poor	1061	8.73	22.63	30.39	12
"	Lime- and phosphoric acid-rich	1011	8.59	23.06	29.89	9

From later experiments it was concluded (Fingerling, 1912b) that neither the activity of the mammary glands nor the composition of the milk was altered by feeding the organic phosphorus compounds.

EFFECTS ON GOAT'S MILK OF ADDING DIFFERENT PHOSPHORUS COMPOUNDS TO A BASAL RATION VERY POOR IN PHOSPHORUS

Fingerling (1912b)—Grams

Date	Ration	Milk		CaO		P_2O_5	
		Total	Gain or loss	Total	Gain or loss	Total	Gain or loss
A	Basal ration	1587	....	1.808	.....	2.594	.....
B	Basal ration	1396	....	3.060	.....	4.164	.....
A	Lecithin added	1515	—72	1.838	+0.030	2.626	+0.032
B	Lecithin added	1563	+167	3.072	+0.012	4.247	+0.083
A	Phytin added	1397	—190	1.813	+0.005	2.555	—0.039
B	Phytin added	1593	+197	3.136	+0.076	4.351	+0.187
A	Casein added	1525	—62	1.784	—0.024	2.531	—0.063
B	Casein added	1606	+210	3.083	+0.023	4.255	+0.091
A	Nuclein added	1491	—96	1.828	+0.020	2.595	+0.001
A	Sodium nucleate added	1430	—157	1.804	—0.004	2.561	—0.033
A	Di-sodium phosphate added	1583	—4	1.883	+0.075	2.656	+0.062
B	Di-sodium phosphate added	1824	+428	3.179	+0.119	4.401	+0.237

Gaube (1895) has also studied this question, and Jensen (1904, 1905a, 1905b, 1905-6) has made extended investigations in this field, especially with rations of varying proportions of hay and beets to which were added phosphates of sodium, calcium and magnesium, etc. Lanzoni (1913) noted slight modifications of composition of milk through the agency of drugs. See also Vivier (1911).

In all cases the variations in phosphorus content of cow's milk which are ascribable to the character of the food are within the range of normal variation. At most these differences are slight, or doubtful, and in no case of practical significance from any point of view.

As to the effects of starvation—the evidence is insufficient to warrant conclusions.

EFFECTS OF DIET ON THE PHOSPHATES OF THE BONES

As the principal store of phosphates in the body the skeleton is of interest in connection with the various circumstances which affect phosphorus metabolism. In judging of the results of experimental feeding, however, we must bear in mind the fact that the amount of phosphorus in the bones is so very much greater than that in the remainder of the body that we may be unable to detect changes of composition in the skeleton under the influence of circumstances which produce marked effects on phosphorus metabolism as revealed by balance experiments. The skeleton is so variable in its development; its mineral constituents are so much affected by the food, that special attention must be given to the breeding and rearing of experimental subjects for comparative studies on the bones. In our own experiments it has been found possible greatly to decrease the central cavity in the shaft of the long bones of pigs by feeding rations which are rich in bone-forming constituents. There seems to be no definite upper limit of phosphate deposit in the bones, as there is in the soft parts.

Chossat (1842) found that pigeons fed on wheat alone died in 8-10 months from malnutrition. The salts were gradually withdrawn from the bones, which became weakened, and the breast bone imperforate. The addition to the diet, of calcium carbonate, appeared to prevent these symptoms, and to maintain the birds in health. Apparently the lack of calcium limited the use of phosphorus. In a later paper Chossat (1843) makes a full report of his experiments with pigeons, chickens, rabbits, frogs, lizards, eels, tortoises, and other animals. The conclusions were in harmony with the above. Where pigeons lost 40.4 percent of the live weight in starving to death, only 3.4 percent of this loss seemed to come from the bony system.

Among other early studies are those of Boussingault (1846a, 1846b), who investigated the effects of foods on the growth of the skeleton of pigs, and C. Falck (1850), who studied the effects of feeding lime-rich and lime-poor foods on the development of domestic fowls.

Dusart (1869) determined that a pigeon lost 4.9 gm. of calcium phosphate from the skeleton, and 58 gm. of live weight during 83 days' feeding on wheat. The addition of calcium carbonate to this diet reduced to zero the alkali phosphates of the excreta, which had been half of the total, and caused a return to the normal live weight.

Dusart (1870) also published clinical reports of 19 hospital cases of fracture or disease of the bones, under treatment with calcium lactophosphate, which he recommends.

Weiske (1871a), in experiments with milch-goats, found that where the food was especially poor in calcium and phosphorus, or in calcium alone, death might be caused by these deficiencies before noticeable change was produced in the composition of the bones. Probably greater refinement of experimental procedure would have demonstrated some change in the bones.

Weiske found (1872a) that calcium, magnesium and strontium phosphates, when fed to rabbits with a ration of hay and turnips, produced no important change in the composition of the ash of the bones.

Weiske and Wildt (1873) fed one lamb on a normal ration, and two more on a basal ration of straw, starch, sugar and casein, which was low in calcium and phosphorus. One of these also received calcium carbonate and the other disodium phosphate. The experiment lasted 25 days. The basal ration seems to have contained enough calcium and phosphorus so that the experimental procedure produced in 25 days no consistent change in the composition of the bones.

Hofmeister (1873) experimented with 8 lambs, 4 in each of two lots, with a low-phosphorus ration of meadow hay and potatoes, to which he added, with one lot, bone phosphates as precipitated from a hydrochloric acid solution by sodium carbonate. The experiment extended from June 7-Nov. 30.

The calcium phosphate caused no appreciable increase in rate of gain in weight. Hofmeister considered that he had proven the digestibility of precipitated phosphates by lambs, by a comparison of food and feces, but attached little importance to the observed increase of phosphorus in the bones of the lambs which had received the phosphates. In the light of subsequent investigation in this

field it would appear that the increase in phosphorus content of the bones, as caused by the inorganic phosphates, was sufficient definitely to increase the breaking strength of the bones. The following data are taken from Hofmeister's tables.

CALCIUM AND PHOSPHORUS CONTENT OF BONES OF LAMBS AS AFFECTED BY ADMINISTRATION OF BONE PHOSPHATES

Dry Matter Basis—Percent

Ration	Jaw bone		Shoulder blade		Humerus		Radius		Tibia	
	P_2O_5	CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5	CaO
Low phosphorus	26.20	31.30	19.60	24.50	19.30	22.60	19.70	23.90	19.70	24.30
Low phosphorus plus bone phosphates	27.80	33.90	20.50	24.90	19.40	22.90	19.90	24.01	20.30	22.60

Hofmeister also studied the digestibility of superphosphate (laboratory prepared), with two 2-year-old wethers, and concluded that, with small doses, all the water-soluble lime and phosphoric acid are digested from superphosphate; with increased doses, one-third of the water-soluble phosphoric acid is digested, while all the water-soluble and half of the insoluble lime is digested. The facts as he noted them, would, of course, be differently interpreted at this time.

Weiske (1874) notes that, of animals receiving the same diet under conditions of practice, some will suffer from fragility of the bones, and others will not. In experiments on rabbits receiving barley and various mineral supplements, Weiske found that the

EFFECTS OF DIET ON THE PHOSPHATES OF THE BONES

Weiske (1874) Percent, Dry, Fat-free Basis

Kind of bone	No. of animals	Mineral matter	P_2O_5	CaO	MgO	Feed	
Fowl, femur	1	45.64	16.67	23.14	0.64	Usual	Normal. Data computed by the compilers.
Fowl, femur	1	42.79	15.98	21.48	0.43	Same	Showed bone disease.
Lamb, pelvic	1	60.46	23.94	31.78		Poor in phosphorus	These are bones of lambs in experiments reported in 1873.
Lamb, pelvic	1	60.36	23.79	31.60		Poor in lime	Data of this experiment computed by the compilers.
Lamb, pelvic	1	60.07	23.94	31.57		Normal	
Rabbit	2	65.64	26.79	34.10	0.75	Calcium-free barley; dist. water	Data computed by compilers.
Rabbit	2	65.08	25.60	33.68	0.76	Same + Mg-phosphate	
Rabbit	2	64.42	26.06	33.34	0.76	Same + Sr-phosphate	
Rabbit	1	65.62	26.26	34.23	0.74	Normal, dist. water	5 mos. old; killed when feeding began.
Rabbit	1	67.61	26.87	35.15	0.80	Normal, dist. water	6½ mos. old; killed at end of experiment.
Rabbit	2	69.03	27.46	35.92	0.79	Normal, dist. water	7½ mos. old.
Rabbit	2	67.55	26.95	35.28	0.73	No food; dist. water	

percentage content of bones, in ash constituents, varied in marked degree, but that the composition of the bone ash remained almost constant. The feeding of magnesium phosphate with calcium-free food did not cause a perceptible increase of magnesium in the bones, and only traces of strontium were found in the ash of the bones of animals to which strontium phosphate was fed. With calcium lacking in the food, an animal lives about as long as if the starvation is total. If the removal of the mineral matter is as complete as possible, there is, as in total starvation, a gradual loss of bone substance.

E. Voit (1880) shows that lack of lime in the diet of dogs reduces not only the lime but also the phosphorus in the bones, as set forth by the following analyses:

ANALYSES OF BONES OF YOUNG DOGS AS AFFECTED BY LACK OF LIME IN THE FEED (E. Voit, 1880)—Percent

Age of pup Days	Bone	Part of bone	Water content of skeleton	Percent of dry substance					Treatment of subject
				Ash	Fe_2O_3	CaO	MgO	P_2O_5	
10	Humerus	Outer	66.2	32.25	0.06	17.04	0.39	12.93	Killed as control
	Scapula	Outer		37.21	....	19.64	0.46	15.45	
	Humerus	Spongy		30.45	0.06	15.92	0.40	12.25	
	Scapula	Spongy		35.01	....	18.19	0.35	14.42	
38	Humerus	Outer	64.9	41.32	0.18	21.40	0.38	17.40	Fed from the age of ten days for 28 days, lime being included
	Scapula	Outer		40.29	0.19	21.40	....	....	
	Humerus	Spongy		33.71	....	16.87	0.28	12.93	
	Scapula	Spongy		36.96	0.31	18.50	0.33	13.62	
38	Humerus	Outer	71.9	30.94	0.16	16.36	0.32	13.17	Fed the same as last, but without lime
	Scapula	Outer		29.06	0.18	15.29	0.38	.....	
	Humerus	Spongy		26.40	0.16	13.34	0.21	10.77	
	Scapula	Spongy		27.22	0.34	14.24	0.19	10.21	

J. Cohnheim (1882) notes that Weiske and others, and Zalesky conclude that the composition of the ash of the bones is not affected by the composition of the food, but that Chossat, Bibra, Wegner, Voit and others have determined that the bones of animals, birds especially, become poor in earth salts and easily bent if the food is poor in these constituents. Young lions and leopards become rachitic when fed on meat without bones (Röll, 1860).

Weiske, Dehmel, Kennepohl, Schulze and Flechsig (1885) fed hay, acidified with sulphuric acid, to sheep, from Nov. 4, 1879 to Mar. 11, 1880, and studied the effects of the acid on the composition of the skeleton. The slight differences, indicating a solution of the bone salts by the acid, were regarded by the authors as within the legitimate error of work. A portion of the data are as follows.

EFFECTS OF ACIDIFIED HAY ON THE COMPOSITION OF THE SKELETON OF SHEEP—Fat and Water Free—Percent

Lamb No.	Feed	Organic matter	Mineral matter	CaO	MgO	CO_2	P_2O_5
1	Normal hay and barley.....	38.16	61.83	31.55	0.66	3.07	24.26
2	Acidified hay and barley.....	39.02	60.98	31.17	0.63	3.02	23.88
3	Killed at beginning of experiment	39.96	60.04	30.34	0.77		23.59

At a later date Weiske (1886) reported more data on this same experiment, and showed that the calcium content of the flesh was decreased by the sulphuric acid feeding, but the phosphorus was not altered; which implies that the effect of sulphuric acid on the bones in the experiment of Weiske, Dehmel, *et al.* (1885) was, at least in part, due to its interference with calcium absorption.

Weiske (1888) experimented to determine the effects of adding, during 6 months, neutral precipitated calcium phosphate to the normal food of rabbits. The phosphate had no effect on the gain in weight, nor on the composition of the bones, though there was a slight increase in the dry fat-free skeleton, due to the use of the phosphate.

Henry (1889, 1890) reported increase in strength and ash of the bones of corn-fed pigs by the administration of bone meal. Wood ashes were found to give similar though less prominent results. Hard-water, in comparison with rain water, was not shown to increase the ash or strength of the bones. No increase of muscle was found (apparently by visual examination) to result from the feeding of bone meal or wood ashes; nor was there increase in the weight of the blood or internal organs.

Beraz (1890) studied the teeth of dogs as affected by the lime content of the ration. Rations producing rachitic conditions in the skeleton generally did not produce similar effects in the teeth.

Weiske (1891a) quotes earlier work showing that dilute sulphuric acid would, if ingested during a considerable time, lower the calcium content of both bones and muscles, and refers to work of Heitzmann, Hofmeister and Siedamgrotzky showing that if lactic acid be given the specific gravity and ash content of the bones is subnormal, and to work of Auerbach showing that KH_2PO_4, when ingested by a dog, greatly increased the ammonia of the urine.

Weiske reports work of his own in which NaH_2PO_4 was fed to rabbits on a ration of meadow hay, oats, beets, and potatoes. The analyses of the skeletons showed no differences of note between the rabbits with phosphate and those without.

At a later date Weiske (1891b) reported further results of a similar but more critical study with rabbits, the rations being (1) hay, (2) oats, (3) hay and oats, and (4) oats and NaH_2PO_4. From the following data it will be noted that the hay was consistently superior, as a bone food, to hay and oats; that the hay and oats were better than oats alone; and that the rabbits appeared to receive benefit from the sodium phosphate, in spite of its acidity.

COMPOSITION OF THE BONES OF RABBITS AS AFFECTED BY THE FOOD (Weiske, 1891b)—Percent, Dry, Fat-free Bone

Bones	No. of animals	Mineral matter	P_2O_5	CaO	MgO	Feed
All	1	64.22	24.89	32.08	0.77	Hay
All	2	63.78	24.82	31.83	0.75	Hay and oats
All	2	61.10	23.90	29.62	1.01	Oats
All	2	61.59	24.47	30.25	0.88	Oats + $Na\ H_2PO_4$
All but long bones and teeth	1	62.13	23.73	30.84	0.68	Hay
All but long bones and teeth	2	61.55	23.69	30.66	0.64	Hay and oats
All but long bones and teeth	2	58.74	22.69	28.47	0.92	Oats
All but long bones and teeth	1	58.47	22.85	28.55	0.67	Oats + $Na\ H_2PO_4$
Long bones	1	66.51	26.02	33.86	0.73	Hay
Long bones	2	66.65	26.15	33.62	0.78	Hay and oats
Long bones	2	62.16	24.85	30.85	0.94	Oats
Long bones	1	63.38	24.94	31.76	0.68	Oats + $Na\ H_2PO_4$
Teeth	1	78.72	33.88	37.28	2.63	Hay
Teeth	2	77.93	33.30	36.73	2.52	Hay and oats
Teeth	2	77.61	33.36	36.18	2.75	Oats
Teeth	1	80.01	34.48	38.08	2.67	Oats + $Na\ H_2PO_4$

Weiske (1892) reported results from feeding rabbits on oats, with trisodium phosphate, monosodium phosphate, tricalcium phosphate, calcium carbonate, and sodium citrate added to the ration, for different lots of animals. The calcium carbonate greatly improved the oat ration. Acid sodium phosphate made the oats less useful than when fed alone, and the effect on the bones was injurious. Benefit was not observed from the other salts.

Arnstadt (1893) discusses malnutrition of the bones of cattle and other farm animals as caused by lack of phosphorus in the food. Pregnant, milk-producing, or young, growing animals were found to suffer most severely. He speaks of liberal allowance of common salt being of benefit when fed with calcium phosphate, through assisting in its assimilation.

Weiske (1895a) fed oats, having an acid ash, to rabbits, with and without other food, except for calcium sulphate and tricalcic phosphate, which were fed to certain individuals. There was a loss of mineral matter from the bones, but no great change in composition. The sulphate and phosphate of calcium proved not to be so valuable as previous experiments had shown the carbonate to be, when added to the same ration.

Weiske (1895c) reports results of feeding experiments on calcium-poor rations, which were rich in phosphorus, and to which were added as supplements, calcium, strontium and magnesium carbonates, and calcium sulphate. The alkaline earth carbonates were found of value in the correction of the acidity of the ash of an oat ration, but magnesium and strontium do not physiologically replace calcium in the skeleton, although not inconsiderable quantities of these elements were transferred there. The urine of the rabbits receiving the alkaline earths was turbid and became continually more alkaline. The rabbit on oats alone had an acid urine. The addition of calcium carbonate was much more beneficial in its effect on the gain in weight than were other mineral supplements.

COMPOSITION OF THE BONES OF RABBITS, AS AFFECTED BY THE FOOD (Weiske, 1895c)—Percent, Dry, Fat-free Bone

Bones	No. of animals	Mineral matter	P_2O_5	CaO	MgO	Feed
All but long bones and teeth..	1	61.34	23.42	31.43	0.73	Oats + $CaCO_3$
All but long bones and teeth..	1	60.17	23.76	30.72	1.11	Oats + $CaSO_4$
All but long bones and teeth..	1	55.47	22.21	23.02	0.61	Oats + $SrCO_3$
All but long bones and teeth..	1	56.98	23.21	28.36	1.39	Oats + $MgCO_3$
All but long bones and teeth..	1	56.62	22.69	28.85	0.63	Oats
Long bones	1	67.14	25.75	34.70	0.85	Oats + $CaCO_3$
Long bones	1	64.58	25.78	32.98	0.76	Oats + $CaSO_4$
Long bones	1	62.59	25.76	27.95	0.96	Oats + $SrCO_3$
Long bones	1	63.89	25.48	32.23	1.48	Oats + $MgCO_3$
Long bones	1	61.73	24.44	31.63	0.74	Oats
Teeth	1	78.66	33.63	38.44	2.40	Oats + $CaCO_3$
Teeth	1	79.35	34.71	38.74	2.61	Oats + $CaSO_4$
Teeth	1	77.58	34.45	36.96	3.23	Oats + $MgCO_3$
Teeth	1	77.74	33.37	37.72	2.57	Oats

Springer (1902) reports that by the application of electricity for 5 minutes daily at the seat of the epiphyseal cartilages of the legs, with rabbits, he induced an added growth of the bones as indicated by the following figures:

		Weight of Femur	Length of Femur
		Grams	Meters
Treated	1	1.105	0.066
	2	1.185	0.064
Controls	3	0.977	0.060
	4	0.940	0.059

Aron (1905) states, with reference to bone diseases of animals, as caused by abnormal food, that with high potassium and low sodium intake, bone formation is held below normal, even though sufficient lime and phosphorus be taken, potassium chloride in solution with primary phosphates apparently tending to prevent their change to di- and tri-calcic salts.

Rasquin (1905-6) fed two young cocks, one with and one without powdered bone, for 120 days. Under the influence of these rations the fowls developed as indicated by the following data:

	A (With Bone)	B (Without Bone)
Weight of body, live	2.690 kg.	2.470 kg.
Weight of body, plucked	2.455 kg.	2.240 kg.
Weight of body, drawn	2.003 kg.	1.790 kg.
Weight of skeleton	236 gm.	190 gm.
Weight of ischium	16 gm.	13 gm.
Weight of bones of wings	41 gm.	30 gm.
Weight of bones of legs	83 gm.	58 gm.
Weight of breast bone	12 gm.	8 gm.
Lime in bones	21.98 pct.	20.51 pct.
Phosphoric acid in bones	18.77 pct.	18.14 pct.
Length of branches of breast bone	13 cm.	9 cm.

Burnett (1906, 1908, 1910) examined the bones of hogs which had received natural foods varying in calcium and phosphorus content, and also others which had received with the food bone meal, calcium carbonate, or disodium phosphate. The development of the bones, as determined by breaking strength, specific gravity, thickness of wall, ash content, etc., reflected the character of the food in the usual way. The principal deposit of bone salts seems to have been inside the marrow space, the walls in this way becoming greatly thickened. Summary tables from three series of observations are quoted on pages 392 and 393.

These tables from the experiments of Burnett show, more plainly than any of the earlier work, the fact that the mineral content of the bones may be modified, in accordance with the composition of the foods, through a very wide range of variation. If this fact appears more prominent in relation to swine than to other animals it is doubtless due to the unusual mineral content of some of the rations used for swine. Through the feeding of precipitated bone flour, which is readily taken by the larger farm animals, it is probably possible to affect the mineral content of their bones also to such extent as to be of practical importance, especially with horses. See also the experiments of Forbes (1909) p. 374.

Alway and Hadlock (1909) compared hog bones produced from corn alone with others produced from corn and bone meal. They state that both lots had practically the same composition, thus indicating that the nature of the food has no effect upon the relative proportions of the different constituents of the mineral matter of

bones. At the same time, considering the bones from corn and bone meal as the standard, the feeding of corn alone is shown, by their ash analyses, to have increased the magnesium by 20 percent, to have increased the phosphorus 1.7 percent and to have decreased the calcium by 1.0 percent of the amounts present. A part of their figures are as follows:

	Weak bones (Corn)	Strong bones (Corn; bone meal)
Average percent mineral matter, green bones	25.4	37.2
Average wall thickness, green bones	2.8 mm.	4.1 mm.
Average breaking strength, green bones	702.0 lbs.	1505.0 lbs.
CaO	52.47 percent	52.98 percent
MgO	1.24 percent	1.05 percent
P_2O_5	41.61 percent	40.93 percent

EFFECTS OF FOODS ON THE BREAKING STRENGTH OF THE BONES OF SWINE (Burnett, 1906)

FIRST TEST

	Lot I	Lot II	Lot III	Lot IV
Killed Feb. 10—				
Number in lot	3	3	3	3
Ration	Soaked corn	Corn 90% Tankage 10%	Corn 90% Ground bone 10 %	Corn 75% Shorts 25%
Av. live weight, lbs.	192	247	257	210
Breaking strength of radius, lbs	723	1308	1561	891
Breaking strength of tibia, lbs	607	825	732	641
Av. of two bones in each leg, lbs	714	1007	1081	783

SECOND TEST

Killed March 14—				
Number in lot	4	4	4	4
Av. live weight, lbs.	171	286	242	204
Breaking strength of radius, lbs	768	1254	1044	835
Breaking strength of tibia, lbs	542	834	779	662
Av. of two bones in each leg, lbs	634	1057	942	801

AVERAGE BREAKING STRENGTH OF BONES PER 100 POUNDS LIVE WEIGHT OF HOGS AT TIME OF SLAUGHTER (Burnett, 1908)—Pounds

Lot	Ration	Femur	Tibia	Humerus	Radius and ulna	All bones
1	Corn	276	252	434	341	325
2	Corn and shorts	343	309	555	376	396
3	Corn and skim-milk	462	360	685	529	509
4	Corn and tankage	559	409	740	611	580
5	Corn and ground bone	646	465	898	715	681

EFFECTS OF FOODS ON THE GROWTH AND STRENGTH OF THE BONES OF SWINE (Burnett, 1910)

SUMMARY FOR TEST OF 1908-1909

Ration	Average live weight Pounds	Average breaking strength of bones in lbs.	Average breaking strength of bones per 100 lbs. live weight of hog	Average length of bones in mm.	Average circumference of bones in mm.	Average weight of bones in gms.	Average volume of bone in c.c.	Average specific gravity of bones	Average wall thickness of bones in mm.	Percentage mineral matter in green bones
Corn	164	763	465	160	68	123	95.5	1.301	4.6	37.88
Corn and alfalfa meal	196	780	398	167	73	143	116.1	1.231	4.8	37.65
Corn, alfalfa meal and shorts	175	822	470	162	69	131	101.6	1.293	4.7	39.55
Corn, alfalfa meal and tankage	193	954	494	167	72	149	110.0	1.361	5.1	41.32
Corn, alfalfa meal and bone meal	171	981	574	168	73	156	114.9	1.363	5.4	42.56

SUMMARY FOR TEST OF 1909-1910

Corn	136	374	275	163	63	104.1	91.3	1.143	2.2	30.04
Corn and lime	144	396	275	168	69	122.0	104.6	1.167	2.3	32.06
Corn and sodium phosphate	155	467	301	169	67	123.3	101.6	1.216	2.7	35.11
Corn and tankage	243	671	276	172	69	136.8	103.8	1.320	3.0	39.89
Corn and bone meal	193	795	412	165	73	143.0	107.6	1.333	4.3	44.15

The above figures represent averages of data from the humeri, radii and ulnae (together), femora and tibiae. This table has been recalculated and corrected by the compilers.

Hart, McCollum and Humphrey (1909), in their study of phytin metabolism with a milch cow, found that when calcium or phosphorus was deficient in the food, the skeletal tissues appeared to be ready sources of supply. The average quantities of calcium oxide and phosphorus pentoxide metabolized and excreted daily during periods of deficient supply were, respectively, 50 and 60 gm.

Schaumann (1910) says, "The idea that the phosphorus eliminated in the urine in pronounced phosphorus starvation comes mainly from bony tissue, as Cathcart thinks, is supported by the findings of Holst with guinea pigs, of Lipschütz and of Heubner with dogs, and by my own with rabbits." (Lipschütz, 1910a; Heubner, 1909; Schaumann, 1908.)

Lipschütz (1910a) studied phosphorus metabolism in dogs with rations varying in phosphorus content. A ration very low in phosphorus produced a moderate increase in weight, but at the end of seven weeks there were protracted muscular cramps and other symptoms of general physiological derangement. An examination of the bones showed a condition which he describes in detail as resembling Barlow's disease. A ration containing the same amount of calcium, but more phosphorus, caused normal development—a case of phosphorus limiting the utilization of calcium. Shortage of calcium limiting the use of phosphorus is much more common in the practical feeding of animals.

R. Berg and C. Rose (1910) state that children and soldiers from regions of hard-water have fewer unsound teeth than others from soft-water regions. The facts may be as stated, but are difficult of satisfactory proof, especially as due to the water.

Dibbelt (1911) reported on experiments on the production and cure of experimental osteomalacia. For several months a dog was kept on a low-calcium diet to which were added disodium phosphate and sodium chloride. At the end of this time the left fourth rib was removed for analysis. Then after 12 days, in which dicalcium phosphate replaced the sodium phosphate, the right fourth rib was removed. For the next 3 months the dog was kept on a mixed diet with liberal allowance of bones. At the end of this period the left fifth rib was removed. During the experiment the dog gave birth to four young. The analysis of the ribs showed that the withdrawal of calcium, as a result of the diet and the bearing of young, caused an atrophy of the bone tissue, and that the administration of the calcium salt, and omission of the salts causing the withdrawal of calcium, with normal feeding, had the effect to replace this loss.

For earlier views on calcification of bone see Aeby (1873b). For other material on the effects of diet on the composition of the bones see Maly and Donath (1873), Weiske (1873, 1891b), Laurer (1910), and Cagnetto (1911); also Hart, McCollum and Fuller (1909), p. 328 of this work, and E. B. Forbes and associates (1914).

Summary on Common Foods in Relation to Phosphorus Metabolism

Our knowledge of the specific effects of common foods in relation to phosphorus metabolism is slight and fragmentary. The evidence, however, is of such nature as to promise important results from further study.

The retention of phosphorus from common foods is, in general, in the same order as the intake, but deficiency of nutrients (as calcium) necessary to the maximum utilization of phosphorus may limit retention, as also may excessive amounts of magnesium in the ration. The deposit of calcium phosphate in the bones is also hindered by inorganic acids, acid salts, calcium-precipitating ions other than phosphorus, and a high potassium and low sodium content of the ration.

The human being stores more phosphorus from whole wheat bread than from white bread.

In comparing diets containing meat and fish, the latter appears more favorable to phosphorus and magnesium retention but less favorable to calcium retention than the former.

White rice does not contain as much phosphorus as the adult human being requires. Red or unpolished rice contains more than enough.

Beet molasses has been thought to increase the solubility and therefore the assimilability of the phosphorus of the ration of the horse.

Young carnivora suffer from malnutrition of the bones if fed on meat alone, to the exclusion of bone.

The low calcium content of cereals and other seeds has been shown, in experiments with growing swine, to limit the retention of phosphorus. The addition of calcium to rations composed of cereal foods serves to increase phosphorus retention.

In experiments with growing swine, comparing many common food during the feeding of skim milk there were minimum proportions of potassium, magnesium, sulphur, chlorine and phosphorus in the feces, and maximum retention of calcium, magnesium, sulphur and phosphorus.

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Experiments with growing swine show that many common foods are lacking in the amount of calcium and phosphorus necessary to maximum production of tissues containing phosphorus.

Foods have been shown to affect the phosphorus content of the muscle, the liver and the kidneys of swine, as related to the ash, the nitrogen and the fresh substance of these parts. The total and inorganic phosphorus of the blood, the lecithin content of the liver, and the composition of the ash of the bones of pigs have also been shown to be susceptible of variation through the influence of corn in the diet.

The bones may be greatly weakened by protracted feeding on foods poor in either calcium or phosphorus, and may be greatly strengthened by the use of foods rich in these elements, the bones appearing to possess an extensive storage function for calcium, magnesium and phosphorus.

Rations which, because of deficiency of mineral salts, cause rachitic changes in the skeleton, have not been shown to produce such effects on the teeth, though it has been stated, with some evidence as a basis, that the salts of the drinking water, in the course of time, may affect the quality of the teeth.

In the effects of diet on the composition of the bones, the ratio of the mineral constituents, one to another, varies but little; there is little replacement possible, for instance, of calcium phosphate by strontium phosphate, though there is some change of proportion of calcium, magnesium and phosphorus in response to the character of the food. The total ash content of the bone may be varied almost at will, by the administration of calcium phosphate or by the use of foods containing the same elements.

Lack of food also affects the phosphorus content of the bones, since these tissues, along with the soft parts, undergo katabolism in starvation.

Calcium phosphate in the diet does not greatly influence gain in body weight, but is readily deposited in the bones, especially within the marrow spaces, having the effect to increase the density and strength of these supporting structures.

The variations in phosphorus content of milk, ascribable to effects of food, are within the range of normal variation.

PHOSPHORUS REQUIREMENTS OF ANIMALS

GENERAL DISCUSSION

In the practical nutrition of human beings, as well as live stock, our interest is especially in conditions of maximum production or efficiency. We never feed for mere maintenance. Maintenance expense is all loss. Our interest is in production, and the amounts and kinds of nutriment necessary to sustain maximum production can with certainty be determined only by production.

Optimum conditions, however, are indefinite and variable. We know almost nothing as to the maximum amounts of phosphorus useful to animals in their various states of life and activity, and are quite unable to submit accurate figures as guides to practice. Maintenance requirements are more accurately known, are less variable with conditions, and hence may be more definitely expressed with safety; but as guides in practical nutrition they must be regarded as irreducible minima, and hence as danger signals, and distinctly not as expressions of the amounts which animals should receive. For real guides to practice we must, for the present, at least, depend in large measure on very general recommendations, and on that judgment which is the result of experience.

Our opinions as to phosphorus requirements of animals are based principally on balances of intake and outgo, and data on elimination during fast. In the use of such observations we must bear in mind, first, that a given amount either of gain or loss of phosphorus in the body ordinarily represents a larger amount of food phosphorus. If an animal gains one gram per day of phosphorus on an intake of 3 grams it would not do to assume that 2 grams represents the maintenance requirement. The one gram of phosphorus retained by the animal represents more than one gram of food phosphorus, because there are certain losses inevitably incident to its utilization, and there would, therefore, be a certain retention of phosphorus, with the above mentioned animal, on a 2.0 gram intake; second, a part of the phosphorus katabolized by the tissues and excreted into the intestine is normally reabsorbed and utilized, as is shown by the fact that the phosphorus loss from the body is less on a phosphorus-free diet than during fast, the reason for which is not definitely known, but which is perhaps connected with the greater absorptive activity in the intestine during the digestion of food than during fast, a fact which would make the fasting loss greater than the minimum maintenance requirement, were it not that this factor is offset by the compensating consideration that a part of the food phosphorus normally escapes digestion.

As a matter of fact these two opposing factors must commonly somewhat nearly balance each other in human nutrition, for the minimum maintenance requirement and the fasting loss happen to be so nearly the same that the one may be used as a measure of the other without great error. This is not necessarily so in animal nutrition generally, however, for were the maintenance requirement determined with foods containing phosphorus in indigestible relations to other nutrients, the loss of indigestible food-phosphorus might exceed the reabsorption of once-digested and excreted phosphorus from the intestine, so that the fasting loss would not equal the maintenance requirement. The phosphorus maintenance requirement of a horse, for instance, would be less on fresh grass than on hay made from the same grass, because of the greater apparent digestibility of the phosphorus of the former than of the latter.

Since it is impossible to feed an animal so as to maintain it in exact phosphorus equilibrium we are obliged to form our judgments as to requirements from data on experiments in which the subject either gained or lost phosphorus. From such data we are unable to state the phosphorus requirement in an exact way, even for the conditions of the experiment, since, as above stated, either gain or loss of phosphorus represents more than the same amount of phosphorus in the food, under ordinary conditions of life. A gram of phosphorus retention, however, represents the same amount of food phosphorus as a gram of loss of phosphorus from the body, and hence by subtracting the retention of phosphorus from the amount in the food, or adding the amount of the loss of phosphorus to the amount in the food, we are able to say that the requirement is less than the former, and greater than the latter. The smaller the retention or loss the more closely will the apparent requirement, calculated as above, approximate the actual requirement under the conditions of the determination.

In order accurately to determine the phosphorus requirements of animals the ration should be so compounded that deficiencies of nutrients other than phosphorus, but essential to the formation of the phosphorus compounds of the body, shall not limit the usefulness of the phosphorus of the food. These conditions are not always observed in studies of this sort, and to this is due a large measure of the variability of the results. It is true that a considerable measure of independence of other nutrients is to be seen in the retention of phosphorus, but at the same time nitrogen and calcium, especially, are so largely used with phosphorus in the body that coincident negative balances of both nitrogen and calcium would in a short time come to exercise a retarding influence on the

Other factors entering into the determination of results of balance experiments with animals are the food habit, as determined by previous feeding, the nature of the particular foods used, and also the kind, age and weight of the subject.

From among the many balance experiments which we might use in this discussion of phosphorus requirements we present a few typical reports of each of the various sorts, without an effort to use them all. On account of the diversity of conditions attending these experiments the computation of mathematical averages would constitute an act of scientific violence of which we desire not to be convicted.

The reader will probably be surprised to note the extremely fragmentary character of the data even on minimum phosphorus requirements of animals, while on optimum requirements we have almost no evidence at all. Most writers, thus far, have been obliged to submit computed estimates only, and as yet there is but slight basis for more definite statements.

PHOSPHORUS EXCRETION DURING FAST

In studying phosphorus excretion during fasting Ajello and Solaro (1893) found, with Giovanni Succi as a subject, that the phosphorus excretion in the urine varied as the loss in body weight, and not as the volume of the urine.

C. Lehmann, *et al.* (1893) showed that the average daily excretion of P_2O_5 in 10 days fasting with Cetti (urine and feces both included) was 2.675 gm.; with Breithaupt the average daily P_2O_5 excretion during 6 days was 2.28 gm.

E. and O. Freund (1901) investigated the proportions of acid, alkaline and earthy phosphates in the urine during fast. The following figures show the results:

FORMS OF PHOSPHORUS IN URINE DURING FAST—Grams P_2O_5

Day of fast	Earthy phosphates	Acid phosphates	Alkaline phosphates	Day of fast	Earthy phosphates	Acid phosphates	Alkaline phosphates	Day of fast	Earthy phosphates	Acid phosphates	Alkaline phosphates
1	0.19	1.60	1.38	8	0.47	1.08	1.23	15	0.46	0.37	0.95
2	0.26	1.41	1.34	9	0.81	0.85	1.55	16	0.36	0.25	0.63
3	0.48	1.40	1.12	10	0.48	0.54	1.14	17	0.39	0.38	0.96
4	0.21	1.48	1.06	11	0.30	0.45	0.96	18	0.32	0.27	0.59
5	0.27	1.46	1.05	12	0.51	0.46	0.89	19	0.33	0.39	0.74
6	0.45	...	...	13	0.35	0.36	0.68	20	0.17	0.26	0.41
7	0.39	0.91	1.22	14	0.41	0.29	0.70	21	0.14	0.23	0.41
Ave. 7 days	0.32	1.21	1.19		0.48	0.58	1.02		0.31	0.31	0.67

From these data it is apparent that, considering the results from a week together, there was during this fast a progressive decrease in both acid and alkaline phosphates, while the earthy

phosphates were the same in amount in the last week as in the first. Averaging these weekly figures shows that for the whole fast the daily excretion of earthy phosphates was 0.37 gm., of acid phosphates 0.70 gm., and of alkaline phosphates 0.96 gm., stated as P_2O_5.

Gilbert and Posternak (1903) state that the loss of phosphorus in the urine of fasting subjects is as follows.

DAILY ELIMINATION OF P_2O_5 IN URINE—Grams per Kilo Body Weight

Man 0.035
Dog 0.065
Cat 0.110

Cathcart and Fawsitt (1907) have given us the following figures on fasting metabolism.

DAILY URINARY EXCRETION OF INORGANIC ELEMENTS DURING FAST

Day of Exp.	P_2O_5 Grams	Cl Grams	S (total) Grams	S (inorganic) Grams	S (neutral) Grams	Acidity C.C. N/10 NaOH	Diet
4	3.60	7.3	1.39	1.17	0.14	579	Egg and milk
5	3.73	5.4	1.41	1.13	0.18	588	Egg and milk
6	4.14	6.7	1.33	1.07	0.15	582	Egg and milk
1	2.26	3.2	0.62	0.44	0.13	378	Fast
2	2.93	2.0	0.93	0.75	0.12	640	Fast
3	2.98	1.5	0.80	0.65	0.12	687	Fast
4	2.91	1.3	0.86	0.69	0.12	604	Fast
6	2.37	1.0	0.71	0.55	0.12	454	Fast
7	1.84	0.84	0.64	0.50	0.11	358	Fast
8	1.89	0.59	0.62	0.49	0.09	344	Fast
10	1.60	0.39	0.56	0.43	0.10	280	Fast
11	1.54	0.30	0.57	0.42	0.12	256	Fast
12	1.55	0.18	0.58	0.44	0.11	212	Fast
14	1.25	0.24	0.54	0.39	0.11	228	Fast
1	0.45	0.53	0.48	0.31	0.12	108	Starch and cream
2	0.20	0.66	0.28	0.14	0.10	88	Starch and cream
3	0.34	0.97	0.29	0.15	0.10	104	Starch and cream
4	0.89	1.10	0.93	0.73	0.16	156	Egg and milk
5	2.10	4.60	0.93	0.74	0.16	263	Egg and milk

Thus the urinary phosphorus excretion during fast varies between 2.98 and 1.25 gm. P_2O_5, the average being 2.10 gm. daily. The decreased excretion of P_2O_5 after the end of the fast is notable, and is coincident with a similar fluctuation in the excretion of sulphur. It doubtless signifies synthesis.

Benedict (1907), in connection with his own work on fasting metabolism, reviews the results of earlier investigations. The following summary is taken from Benedict's discussion. The black-faced type signify the quotient $N:P_2O_5$.

DAILY PHOSPHORUS (P_2O_5) EXCRETION AND RATIO BETWEEN NITROGEN AND PHOSPHORUS EXCRETION IN URINE OF FASTING SUBJECTS—Grams

Day of fast	Succi			Cetti	Breit-haupt	J	Sohn	Subject I	Flora Tosca	Keller
	At Florence	At Naples	At Vienna							
Last day of food		**4.73**		**4.89**	**4.84**	**7.40**	**6.21**	**4.53**	**5.24**	**4.41**
		1.90		2.76	2.69	1.682	3.381	1.58	2.670	1.86
1	**7.87**	**4.90**	**5.70**	**5.22**	**6.42**	**5.20**	**5.37**	**3.97**	**5.65**	**3.55**
	1.930	1.78	2.98	2.597	1.56	1.091	2.303	2.22	1.550	1.90
2	**5.91**	**4.64**	**4.07**	**4.30**	**5.25**	**6.51**	**5.45**	**3.81**	**4.58**	**3.24**
	2.051	1.82	2.75	2.925	1.89	1.491	2.268	2.65	1.830	2.44
3	**7.30**	**4.64**	**4.19**	**3.99**	**5.25**	**6.03**	**6.17**	**4.41**	**4.04**	**4.54**
	2.090	1.95	2.52	3.289	2.53	1.571	2.270	2.65	2.654	2.53
4	**6.64**	**5.83**	**4.25**	**4.17**	**5.42**		**5.54**		**3.20**	
	2.120	1.46	2.54	2.974	2.36		5.052		2.934	
5	**5.90**	**3.74**	**4.46**	**3.73**	**5.00**				**4.50**	
	2.394	2.64	2.51	2.871	2.19				1.749	
6	**5.18**	**3.49**	**4.85**	**3.79**	**4.32**		**4.43**		**7.23**	
	2.150	2.47	2.27	2.667	2.29		2.434		1.069	
7	**5.53**	**3.28**	**4.13**	**4.09**			**4.60**		**8.57**	
	1.865	2.32	2.13	2.663			3.150		0.713	
8	**5.85**	**4.18**	**4.22**	**5.17**			**4.86**		**4.64**	
	1.601	1.48	2.31	1.722			4.442		1.658	
9	**6.29**	**4.63**	**4.19**	**5.24**					**4.32**	
	1.360	1.49	2.40	2.065					1.702	
10	**5.96**	**4.37**	**4.24**	**10.00**					**4.65**	
	1.246	1.23	1.68	0.948					1.461	
Av. ratio $N:P_2O_5$	**6.24**	**4.37**	**4.43**	**4.97**	**5.28**	**6.29**	**5.20**	**4.06**	**5.14**	**3.94**

The following table sets forth results from Benedict's investigation.

RATIOS OF NITROGEN TO PHOSPHORUS (P_2O_5) AND AMOUNTS OF PHOSPHORUS EXCRETED IN THE URINE DURING FAST

Grams

Exp. No.	Subject and duration	First day	Second day	Third day	Fourth day	Fifth day	Sixth day	Seventh day	Initial body wt. Kg.
69	A. L. L., Dec. 16-19	**10.78**	**11.96**	**14.19**	**12.44**				73.806
		0.936	1.192	1.060	1.043				
71	S. A. B., Jan. 7-10	**7.93**	**8.33**	**6.55**	**5.27**				58.199
		0.736	1.326	2.000	2.038				
73	S. A. B., Jan. 28-Feb. 1	**4.39**	**6.29**	**5.96**	**4.81**	**4.68**	**5.19**	**4.87**	59.134
		2.345	1.904	1.938	2.159	2.134	2.071	2.081	
75	S. A. B., Mar. 4-10	**8.55**	**5.52**	**6.34**	**4.83**	**5 23**			59.520
		1.431	2.255	2.055	2.406	2.078			
77	S. A. B., Apr. 8-11	**4.71**	**3.90**	**4.41**	**4.35**				61.612
		1.871	2.763	2.492	2.634				
79	H. E. S., Oct. 13-14	**7.50**	**8.62**						57.170
		1.081	1.664						
80	C. R. Y., Oct. 27-28	**6.57**	**4.11**						69.342
		1.184	2.421						
81	A. H. M., Nov. 21-22	**6.19**	**5.37**						62.016
		1.472	2.430						
82	H. C. K., Nov. 24-25	**8.43**	**7.18**						71.493
		1.113	2.000						
83	H. R. D., Dec. 5-6	**5.51**	**4.84**						55.637
		2.407	2.793						
85	N. M. P., Dec. 9-10	**8.79**	**9.55**						67.625
		1.257	1.189						
89	D. W., Jan. 10-11	**4.24**	**4.61**						79.063
		2.354	3.134						
	Average	**6.97**	**6.69**	**5.82**	**4.82**				
		1.516	2.089	1.909	2.056				

Body weight in Exp. 69-77 includes underclothing, Exp. 80 all clothing, Exp. 79, 81 and 82-89, no clothing.

From the two foregoing tables we note that the phosphorus excretion is usually higher on the second day than on the first; that after the second day there is little regularity in the variations; that there is a progressive decrease in the factor $N:P_2O_5$, at least during the first four days, which may be due to autolysis of bone tissue, and that the daily elimination of phosphorus (P_2O_5) in the urine of the fasting man is about 2.00 grams.

Benedict included in his study of fasting metabolism balance determinations in the period following the fast. The following nitrogen and phosphorus data exhibit marked initial retention followed by progressive decrease to the normal.

AVERAGE DAILY NITROGEN AND PHOSPHORUS (P_2O_5) BALANCES WITH HUMAN SUBJECTS FOLLOWING A FAST—Grams

Exp. No.	Week No.	Nitrogen				Phosphorus (P_2O_5)			
		Food	Urine	Feces	Balance	Food	Urine	Feces	Balance
1	1	21.11	10.60	2.35	+8.17	10.712	1.804	2.015	+6.893
1	2	21.80	10.56	3.88	+7.36	8.699	2.673	2.787	+3.238
1	3	17.38	11.40	2.79	+3.19	5.899	3.097	1.983	+0.819
1	4	15.67	11.86	2.54	+1.27	5.588	2.795	1.865	+0.928
2	1	19.61	14.13	2.46	+3.02	5.889	2.256	2.235	+1.398
2	2	19.41	12.48	2.36	+4.57	5.907*	2.913*	1.985*	+1.009

* For six days.

Phosphorus determinations on urine of Exp. I were made by the uranium acetate method; those of Exp. 2 were made by fusion.

Halpern (1908) obtained data as follows on the urinary excretion of a man who was about to die with cancer. The urine for two days, during which no nutriment other than 30 gm. grape sugar in 600 c.c. of water was taken, contained the following constituents per day: Total N, 2.058 gm. (after deducting albumin, 2.0097 gm.); ammonia N, 0.0714 gm., or 3.47 percent of the total N; purin N, 0.059 gm.; SO_3, 0.344 gm., and P_2O_5, 0.319 gm. The ratio of N to P_2O_5, therefore, was as 6.3:1.

Summary. The phosphorus excretion of an adult human being during fast is about 2.00 gm. P_2O_5; the excretion varies in general with the loss in weight. There is in fast a progressive decrease in acid and alkaline phosphates in the urine; the earthy phosphates show first an increase, and subsequently a return to the earlier figures. There is, at least during the first four days of fast, a progressive decrease in the proportion of nitrogen to phosphorus in the urine. The phosphorus excretion immediately subsequent to

fast may be much less than during fast. The retention of phosphorus after the cessation of fast is very marked but gradually returns to the normal.

For a discussion of other phases of phosphorus metabolism during fast see P. Met. During Fast.

NORMAL PHOSPHORUS REQUIREMENTS OF ADULT HUMAN BEINGS

Siewert (1868) publishes results of nitrogen balance experiments with human subjects, balance data on inorganic elements also being included in some cases. A part of the results are set forth below.

AVERAGE DAILY NITROGEN, CALCIUM AND PHOSPHORUS BALANCES WITH A HUMAN SUBJECT ON A NORMAL MIXED DIET—Grams

Experiment No.	N Food Urine Feces Balance	CaO Food Urine Feces Balance	PO_5 Food Urine Feces Balance	Body weight Initial Final
2	19.051 15.844 2.788	1.093 0.209 0.963	4.932 3.265 1.740	56000
Feb. 10-19	+0.419	−0.079	−0.073	55450
3	19.360 15.682 2.563	1.026 0.188 0.880	5.441 3.118 2.381	55600
Mar. 2-11	+1.115	−0.037	−0.058	56750

The negative phosphorus balances must have been due to a well-established habit of excessive phosphorus intake and outgo, because the intake, in amounts as above stated, is usually ample for maintenance purposes.

Platt (1897) submits the following data for the average daily urinary phosphorus of adult Americans. The figures, of course, represent food habit more accurately than food requirement.

PHOSPHORUS IN NORMAL HUMAN URINE—Grams in 24 Hours

	Normal urine	Man	Woman
Total phosphorus (P_2O_5)	2.0—3.5	3.0	2.5
Glycerophosphoric acid	0.01—0.02	0.015	

See also Krabbe (1857).

Siven (1901) reported results of metabolism experiments on a man who was 31 years old, and who weighed normally about 65.2 kg., with rations of normal foods so chosen as to vary the protein content of the diet. A portion of the numerical data are given below.

DAILY PHOSPHORUS BALANCES OF A MATURE MAN ON RATIONS VARYING IN PHOSPHORUS CONTENT—Grams

Date	Food	Urine	Feces	Balance	Urine and Feces	Diet
Nov. 14	0.526	0.458	0.283	0.741	−0.215	Potatoes, apples, butter, sugar, beer
" 21	0.526	0.356	0.331	0.687	−0.161	" " " " "
" 22	0.644	0.389	0.364	0.753	−0.109	" " " " " eggs
" 23	0.644	0.381	0.364	0.745	−0.101	" " " " " "
" 24	0.644	0.437	0.364	0.801	−0.157	" " " " " "
" 25	0.644	0.523	0.364	0.887	−0.243	" " " " " "
" 26	1.131	0.654	0.460	1.114	+0.017	" " " " " "
" 27	1.653	0.887	0.460	1.347	+0.306	" " " " " "
" 29	1.653	0.978	0.460	1.438	+0.215	" " " " " "
Dec. 1	1.629	0.802	0.460	1.262	+0.367	" " " " " "
" 2	1.558	0.964	0.460	1.424	+0.134	" " " " " "
" 3	3.183	1.108	1.595	2.703	+0.480	Bread, milk, eggs, cheese, butter, apples, beer
" 4	3.124	1.410	1.595	3.005	+0.119	" " " " " " "
" 5	3.124	1.441	1.595	3.036	+0.088	" " " " " " "
" 6	3.099	1.410	1.595	3.005	+0.094	" " " " " " "
" 7	3.194	1.445	1.595	3.040	+0.154	" " " " " " "
" 8	3.147	1.441	1.595	3.036	+0.111	" " " " " " "

From these data the author concludes that the minimum daily requirement of phosphorus of the adult human being is about 0.7-0.8 gm. From the data of Nov. 22-Dec. 2 we compute that with this subject the requirement was more than 0.8 and less than 1.3 gm. P.

Ehrström (1903b) succeeded in maintaining phosphorus balance during 13 days in a woman 40 years old solely by the use of rectal injections of milk and a casein-containing preparation, "proton," the phosphorus intake per day being 0.61 gm. during 8 days, and 0.91 gm. during the last 5 days. The phosphorus absorbed during the first 8 days was 0.42 gm. per day, and during the last 5 days 0.74 gm. per day.

In another case, a man 42 years old, the injection of 1.22 gm. P, and absorption of 0.51 gm., did not maintain equilibrium; loss per day 0.530 gm. P.

A third case, a woman 31 years old, was not maintained in phosphorus equilibrium by a rectal intake of 1.22 gm. P per day, and an absorption of 0.71 gm.; loss per day 0.19 gm. P.

The result with the first mentioned case suggests the high efficiency of casein phosphorus.

Maurel (1901, 1904) in experiments on himself, with normal diet, concluded that the phosphorus requirement of the human being is 0.04-0.05 gm. P_2O_5 per kg. of body weight. In this connection he considers also the content of P_2O_5 in human milk, which is

stated to be 0.05 gm. P_2O_5 per 100 gm. of milk, which is about the amount consumed by infants per kilogram of body weight per day. Since Maurel's experiments had to do with urinary excretion alone they hardly furnish a basis for a close estimate of the phosphorus requirement.

In balance experiments on a diet of crackers, butter and milk, with a man weighing 60 kg., Sherman (1902) found, in 4- and 5-day periods, that in two experiments there was a negative balance on an intake of 1.58 gm. phosphorus; again a negative balance on an intake of 1.4 gm. phosphorus, and a positive balance on an intake of 1.6 gm. phosphorus. These amounts appear to be close to the phosphorus requirement under normal conditions.

From the work of Ehrström (1903a) (see p. 322) it would appear that under the conditions of the second period of his experiment phosphorus equilibrium could have been maintained on less than 1.348 gm. P.

Renvall (1904), experimenting on himself, at an age of 22 years and weight of 71.1 kg., found in a series of balance experiments with a normal mixed diet, that in a 5-day period the average daily phosphorus loss was 0.030 gm. on an intake of 2.103 gm. of P_2O_5, the most that was fed during any period in the series. The requirement, therefore, seems to have been more than 2.133 gm. P_2O_5.

Gilbert and Posternak (1903) failed to maintain P_2O_5 equilibrium on an intake of 2.43 gm. daily, but with an addition of lecithin, bringing the intake up to 2.745 gm., as an average of a 3-day period, there was a retention of 0.031 gm. P_2O_5 per day; thus under these conditions the phosphorus requirement was apparently less than 2.714 gm. P_2O_5.

In the course of their investigations of the influence of food preservatives and artificial colors on digestion and health, Wiley, and associates (1904, 1906, 1907, 1908a, b) accumulated a large amount of balance data which are not without value as indications of the phosphorus requirements of human beings. The experiments were all on healthy young men, and for the purpose of this discussion we submit average daily balances of the groups used in the several investigations, the data covering the fore-periods only, during which no preservatives were fed.

One circumstance requires mention as bearing on the accuracy of these balances. The feces were not marked at the beginning and end of the experimental periods. The large number of subjects

and periods, however, tends to reduce the error, though the periods, being 5-10 days in duration, were too short to be really satisfactory for our purpose. The food was normal and varied in character.

AVERAGE DAILY PHOSPHORUS BALANCES WITH HEALTHY YOUNG MEN—GRAMS P_2O_5

Number of subjects	Number of periods	Body weight Kg.	Food	Urine	Feces	Balance	Publication
12	30	66.14	4.358	2.648	1.571	+0.139	Bu. Chem. Bul. 84, Part I
9	9	62.71	3.816	2.364	1.247	+0.205	" " " " " II
12	12	63.69	4.312	2.455	1.352	+0.508	" " " " " III
11	11	63.27	3.782	2.244	1.047	+0.491	" " " " " IV
10	10	63.30	3.956	2.375	1.262	+0.319	" " " " " V

These data show that a free choice of normal foods provides a considerable excess of phosphorus, and that these young men of somewhat under average weight naturally took in the food 3.78-4.36 gm. of P_2O_5.

VonWendt (1905) finds that if the human body receives a sufficient amount of oxidizable nitrogen-free material, the outgo of nitrogen, sulphur and salts may be considerably decreased, through the establishment of an internal circulation by means of which these substances are retained in the body and are available for repeated use. VonWendt states that the body maintenance requirement of phosphorus (P) is about 0.010 gm., of calcium 0.008 gm., and of magnesium not more than 0.001 gm. per kilogram of body weight.

Experiments of Hawk (1905), with two normal mature men weighing 61.4 and 62.8 kg., on a diet of crackers, butter and milk showed that with an intake of 4.96 gm. P_2O_5 daily there resulted a storage of 0.145, 0.279 and 0.207 gm. P_2O_5 in 2-day periods. These individuals were living on a plane of phosphorus metabolism which did not require economy by the body.

With a 30-year-old man Gilbert and Posternak (1905) failed to maintain phosphorus equilibrium on an intake of 3.19 gm. P_2O_5 daily, but got a storage of 0.121 gm. P_2O_5 on an intake of 3.43 gm. P_2O_5 daily, the requirement thus appearing to be less than 3.31 gm. P_2O_5.

In experiments by Gumpert (1905) an adult man lost 0.018 gm. P_2O_5 per day on an intake of 1.885 gm. in a 5-day period, the phosphorus requirement, therefore, appearing to be greater than 1.903 gm. P_2O_5. The diet was of normal mixed foods plus casein. In other periods, containing meat instead of casein, the phosphorus requirement seems to have been much greater.

E. Koch (1906) studied phosphorus metabolism in a man weighing 63.9 kg. On a normal mixed ration, in a four-day period, with a phosphorus intake of 4.43 gm. P_2O_5 daily, the storage was 0.34 gm. daily, the intake, therefore, being too much in excess of the minimum to afford critical evidence as to actual requirement.

Robert and Parisot (1906) quote from the tables of Roche, *et al.* the following statement of the normal phosphorus content of the urine of people from middle life to old age. These figures reflect especially the diminished food consumption accompanying decreased activity.

PHOSPHORUS OF NORMAL HUMAN URINE

Age	Grams P_2O_5 for 24 hours
54–59	1.85
60–64	1.46
65–69	1.35
80–85	1.0-1.10

Hämätäinen and Helme (1907) conducted a series of one-day balance observations with rations of very low phosphorus content. The daily phosphorus balances are as follows:

PHOSPHORUS METABOLISM ON A LOW-PHOSPHORUS DIET WITH SUPPLEMENTS ADDED AT INTERVALS

Daily Balances in Grams P

Day	Food	Urine	Feces	Balance	Remarks
1	0.377	0.683	0.244	−0.550	
2	0.324	0.666	"	−0.586	
3	0.524	0.639	"	−0.359	
4	0.586	0.630	"	−0.288	
5	0.517	0.427	"	−0.154	
6	0.536	0.407	"	−0.115	
7	0.705	0.350	"	+0.153	800 gm. egg white=0.114 gm. P
8	0.604	0.418	0.202	−0.046	
9	0.573	0.436	"	−0.065	
10	0.567	0.367	"	−0.002	
11	0.551	0.512	"	−0.163	
12	0.559	0.366	"	−0.009	
13	0.552	0.439	"	−0.089	
14	0.565	0.443	"	−0.080	
15	0.554	0.401	"	−0.049	
16	1.040	0.663	0.255	+0.122	57 gm. proton=0.479 gm. P
17	0.559	0.368	"	−0.064	
18	0.552	0.390	"	−0.093	
19	0.557	0.393	"	−0.091	
20	1.186	0.739	0.233	+0.214	320 gm. roast veal=0.627 gm. P
21	0.557	0.518	"	−0.194	
22	0.555	0.473	"	−0.151	
23	0.535	0.355	"	−0.053	

On the strength of the records of the 8th, 10th and 12th days the authors state that the body is able to maintain a phosphorus balance on 0.55-0.65 gm. phosphorus per day. We would suggest, however, that on 12 other days, with an intake of 0.55-0.60 gm., there was decided loss of phosphorus. These figures show such a daily variation in phosphorus outgo that we may be warned against drawing conclusions from single day's balances.

In experiments by Oeri (1909), a man 25 years old, weighing 93 kg., and engaged in laboratory work, failed to maintain phosphorus equilibrium on 6.54 gm. P_2O_5 intake daily in a normal mixed diet. The addition of 2 gm. P_2O_5 as disodium phosphate resulted in marked storage. On approximately the same kind of diet a woman 35 years old, and weighing 55 kg., stored something like half of a gram of P_2O_5 daily on an intake of 5.45 gm. P_2O_5. Neither of these subjects was using phosphorus economically.

Hoffström (1910), in studying metabolism in pregnancy, determined that during 24 weeks, the 17th-40th of pregnancy, with an average daily intake of 1.952 gm. phosphorus, the average daily storage was 0.331 gm.

Sherman, Mettler and Sinclair (1910), in a series of 6 three-day balance experiments on a healthy man studied calcium, magnesium and phosphorus metabolism. A portion of the results are in the following table (p. 409).

Nitrogen on feces was estimated from previous work. The two rations which came nearest to maintaining phosphorus equilibrium were Nos. 1 and 6 where, with incomes of 1.546 gm. and 1.509 gm., respectively, the loss was 0.054 gm. and 0.015 gm. of phosphorus, the requirement, therefore, apparently being more than the intake plus the loss, or 1.6 gm. and 1.524 gm.

The authors conclude: "From the results here obtained, as well as the average results of experiments by other observers, it would appear that a healthy man, accustomed to full diet of the ordinary mixture of animal and vegetable food materials, requires for the maintenance of his ordinary store of phosphorus compounds about 1.5 gm. of phosphorus, or nearly 3.5 gm. of P_2O_5 per day, though under special conditions or with a specially selected dietary, equilibrium may be maintained on much less, (0.9 gm. phosphorus or about 2.0 gm. P_2O_5)."

AVERAGE DAILY BALANCES OF NITROGEN, CALCIUM, MAGNESIUM AND PHOSPHORUS WITH AN ADULT MAN ON A SIMPLE DIET

Grams

Experiment No.	Initial and final body weight Lbs.	Fuel value Cal.	N Food / Urine / Feces / Balance	Ca Food / Urine / Feces / Balance	Mg Food / Urine / Feces / Balance	P Food / Urine / Feces / Balance	Diet
1	143-137.5	1690	10.10 / 13.09 / 0.46 / −3.45	2.651 / 0.210 / 1.880 / +0.561	0.286 / 0.190 / 0.170 / −0.074	1.546 / 1.030 / 0.570 / −0.054	150 gm. crackers, 1500 gm. milk
2	137.5-137.5	1833	10.69 / 13.21 / 0.75 / −3.27	0.139 / 0.097 / 0.480 / −0.438	0.113 / 0.130 / 0.080 / −0.097	0.384 / 0.753 / 0.223 / −0.592	400 gm. crackers, 250 gm. coagulated white of egg
3	138-136	1930	7.02 / 10.29 / 0.70 / −3.97	0.126 / 0.054 / 1.230 / −1.158	0.079 / 0.093 / 0.126 / −0.140	0.401 / 0.695 / 0.452 / −0.746	450 gm. crackers
4	136-139	2774	9.41 / 9.95 / 0.77 / −0.91	0.948 / 0.108 / 0.716 / +0.124	0.160 / 0.132 / 0.053 / −0.025	0.836 / 0.659 / 0.226 / −0.049	450 gm. crackers, 450 gm. milk, 75 gm. butter
5	139-137.5	2140	7.00 / 8.54 / 0.54 / −2.08	0.866 / 0.188 / 0.582 / +0.096	0.132 / 0.138 / 0.046 / −0.052	0.702 / 0.790 / 0.160 / −0.248	300 gm. crackers, 450 gm. milk, 75 gm. butter
6	137.5-137	2170	11.64 / 10.59 / 0.68 / +0.37	2.237 / 0.307 / 1.807 / +0.123	0.263 / 0.179 / 0.141 / −0.057	1.509 / 0.992 / 0.502 / −0.015	300 gm. crackers, 1350 gm. milk

Sherman *et al.* (1910) compute the following estimates of the ash constituents of typical American dietaries.

ESTIMATED AVERAGE DAILY QUANTITIES PER MAN OF CERTAIN CONSTITUENTS IN TYPICAL AMERICAN DIETARIES—Grams

Persons studied	Fuel value Cal.	Protein	Fe	P_2O_5	CaO	MgO
Maine lumbermen	6780	179	0.035	5.88	1.27	1.21
School superintendent's family, Chicago	3260	123	0.021	3.97	1.09	0.55
Student's club, Univ. of Tennessee	3595	123	0.019	4.05	1.22	0.63
Decorator's family, Pittsburgh	3305	112	0.019	3.44	0.90	0.48
Farmer's family, Connecticut	3545	108	0.021	3.53	1.15	0.55
Teacher's family, Indiana	2780	106	0.016	3.64	1.42	0.44
Teacher's family, New York City	3180	102	0.016	3.92	1.69	0.54
Mechanic's family, Tennessee	4060	97	0.017	3.58	0.90	0.72
Farmer's and mechanic's family, Tennessee	2820	95	0.019	3.56	0.83	0.59
Glassblower's family, Pittsburgh	3085	94	0.016	2.73	0.49	0.36
Lawyer's family, Pittsburgh	3280	91	0.015	2.82	0.83	0.40
Women students' club, Ohio	3330	85	0.015	2.88	0.97	0.67
Laborer's family, New York City	2335	84	0.014	2.41	0.47	0.30
Laborer's family, Pittsburgh	2525	83	0.013	2.40	0.50	0.34
Negro farmer's family, Alabama	4955	80	0.012	3.25	0.21	0.74
Laborer's family, Pittsburgh	2440	77	0.012	1.52	0.40	0.19
Laborer's family, New York City	2430	71	0.012	2.27	0.50	0.29
Farm students' club, Tennessee	3560	66	0.011	2.08	0.46	0.34
Sewing woman's family, New York City	1500	54	0.009	1.84	0.68	0.23
Very poor negro family, Alabama	2240	44	0.007	2.05	0.08	0.52

The authors comment on these figures in part as follows: "Many of the dietary studies show so much less than 3.5 gm. of P_2O_5 per man per day as to raise a question whether these people may not have been undernourished in this respect, even though they may have had ample proteins, fats and carbohydrates."

Holsti (1910), experimenting on himself at a weight of 58 kg., and age of 21 years, retained 0.007 gm. P under normal conditions on an intake of 2.57 gm. daily during a 3-day period. With a subnormal nitrogen intake, which gave a minus nitrogen balance, he retained 0.185 gm. P on an intake of 1.922 gm. daily in a 6-day period, the requirement in the latter case appearing to be less than 1.737 gm.

Aron and Hocson (1910) studied phosphorus metabolism in connection with beriberi. From experiments on two normal individuals it was determined that a diet consisting of fish, bread, rice, sugar, etc., furnishing 37 calories, 0.2 gm. nitrogen, and 0.032 gm. P_2O_5 per kilo of body weight, is sufficient to keep a man in N and P_2O_5 equilibrium.

VonWendt (1910), in a series of 1-day balance experiments on himself, at different altitudes in the Alps, seems, on a number of days, to have retained phosphorus on an intake of 0.861 gm. P, but on a greater number of days there were losses of phosphorus greater in magnitude than the previously mentioned storage. We must conclude therefore, that under his conditions 0.861 gm. P was an insufficient amount. The calcium balances were negative, and the nitrogen balances positive.

R. Tigerstedt (1911) studied the composition of the freely-chosen food consumed by 64 persons ranging in age from 2 years to maturity. Some of his results are set forth in the following table.

AVERAGE DAILY CALCIUM, MAGNESIUM AND PHOSPHORUS OF THE FREELY CHOSEN DIETS OF HUMAN BEINGS OF VARIOUS AGES
Grams

	P_2O_5	CaO	MgO
Children 2-3 years	1.18	1.58	0.24
Children 4-7 years	1.93	1.84	0.39
Children 8-11 years	2.55	2.37	0.59
Girls 12-16 years	3.09	2.21	0.89
Boys 12-16 years	3.09	2.01	0.71
Adult women	2.77	2.29	0.66
Adult men	4.33	3.79	1.09

Tigerstedt states his opinion that the P_2O_5 intake, in order to maintain the phosphorus balance, should be from 2.0 to 3.5 gm. per day. From his investigations it appears that the adult man's diet contains more than this amount (mean 4.33 gm.), while adult women at moderate labor consume 3.57 gm. daily. The phosphorus values

varied within wide limits (P for men 2.80-6.01 gm., women, 1.69-4.26 gm.).

In connection with their study of rice as the cause of beriberi, Aron and Hocson (1911a, 1911b) report the following experiments with healthy men.

PHOSPHORUS BALANCES ON HEALTHY MEN

No. of period	Length of period in days	Foodstuffs	Calories per kg. body wt.	P_2O_5 intake per kg. body wt.	P_2O_5 of urine, percent of intake	P_2O_5 of feces, percent of intake	Body wt. Kg.	P_2O_5 balance Grams
3	4	Rice[1], sugar, bacon, coffee, onions, fat....	44	.066	32.0	63.1	49.0	+0.16
4	4	Rice[2], bread, sugar, bacon, coffee, onions, fat	45	.029	73.2	58.4	48.6	−0.45
5	4	Rice, bread, sugar, bacon, coffee.....	41	.023	100.0	48.7	64.0	−0.97
6	4	Rice, bread, sugar, bacon, coffee, phytin.	41	.077	31.7	37.7	64.0	+1.50
7	4	Rice, bread, sugar, bacon, coffee, egg white	41	.029	83.5	32.4	64.0	−0.30
8	4	Rice, fish, sugar, coffee, bananas.....	39	....	....	....	54.0	....
9	6	Rice, bread, fish, sugar, coffee.....	38	.033	62.5	38.0	43.5	−0.01
10	4	Rice, bread, fish, sugar, coffee.....	37	.032	72.6	33.7	52.5	+0.01[3]
11	4	Rice, bread, fish, sugar, coffee, wheat flour	37	.104	25.3	63.4	52.5	+0.62
12	3	Rice, bread, fish, sugar, coffee.....	31	.033	57.6	42.9	54.0	−0.22
13	3	Rice, bread, fish, sugar, coffee.....	31	.033	57.6	41.2	54.0	−0.10
14	4	Rice, bread, fish, sugar, coffee.....	30	.032	65.5	40.0	45.9	−0.08
15	4	Rice, bread, fish, sugar, coffee.....	30	.031	74.2	....	53.0	....

(1) Red rice, that is, only hulled.
(2) White rice, overmilled.
(3) —0.09 according to our calculations.

Authors' conclusions:

An intake of 1.65 gm. P_2O_5 per 50 kg. body weight, or less, does not cover the body requirement. The body loses phosphorus on a white rice diet, but gains on the "red" rice (hulled only).

Herbst (1912) conducted balance experiments on 7 normal boys 6-14 years old. The phosphorus consumption was 3 gm. P_2O_5 per day, of which half was recovered in the urine, and one-fifth in the feces; the remainder (0.5-1.0 gm. per day) was retained. The calcium and phosphorus balances from 6 of these boys, on an ordinary mixed diet, in abundance, are in the following table (p. 412). The data represent averages per day for 6-day periods.

Herbst (1913) studied growth in two boys aged about 14 years. On a normal mixed diet, controlled by weights and analyses, the boys were subjected to a 5-months period of observation on growth and weight, in the midst of which was a 12-day balance experiment during the first 6 days of which the subjects took long walks, and during the last 6 of which they took only normal exercise. On p. 413 are a part of the balance data, which we have calculated to average figures per day.

During ordinary activity phosphorus was stored in considerable amounts, the intake being 0.073 and 0.067 gm. P_2O_5 per kilogram of body weight. With more liberal intake of calcium the phosphorus retention might have been greater.

DAILY NITROGEN, PHOSPHORUS AND CALCIUM BALANCES WITH GROWING BOYS ON AN ORDINARY MIXED DIET—Grams

Age	Wt. Kg.		N Retention	Phosphorus (P_2O_5) balances				Calcium (CaO) balances			
				Intake	Urine	Feces	Retention	Intake	Urine	Feces	Retention
yrs. 0 mos...	26.8	abs.	2.078	3.3636	1.4695	0.7119	1.1822	1.1907	0.1891	0.6263	0.3752
		per kg.	0.077	0.1256	0.0548	0.0265	0.0442	0.0445	0.0070	0.0233	0.0142
yrs. 7 mos...	41.2	abs.	1.881	3.8659	2.0450	0.7069	1.1140	1.3854	0.1300	0.8107	0.4447
		per kg.	0.045	0.0937	0.0495	0.0172	0.0270	0.0335	0.0032	0.0197	0.0107
yrs. 6 mos...	21	abs.	1.197	2.6878	1.4072	0.6421	0.6385	0.9948	0.1517	0.5408	0.3024
		per kg.	0.057	0.1280	0.0670	0.0310	0.0303	0.0473	0.0072	0.0257	0.0143
yrs. ½ mo..	24.3	abs.	1.082	3.0491	1.6098	0.5362	0.9031	1.1084	0.0391	0.5227	0.5465
		per kg.	0.044	0.1255	0.0663	0.0220	0.0372	0.0457	0.0015	0.0215	0.0227
yrs. 6 mos...	22.1	abs.	1.297	3.0232	1.7117	0.5987	0.7128	1.0721	0.0770	0.6084	0.3867
		per kg.	0.058	0.1365	0.0773	0.0270	0.0322	0.0483	0.0035	0.0275	0.0173
yrs. 5 mos...	20.9	abs.	0.400	2.6367	1.6522	0.5257	0.4589	1.0288	0.2620	0.4781	0.2887
		per kg.	0.019	0.1263	0.0792	0.0251	0.0220	0.0492	0.0125	0.0228	0.0139

AVERAGE DAILY NITROGEN, CALCIUM AND PHOSPHORUS BALANCES WITH TWO GROWING BOYS—Grams

Boy No.	Body weight Initial Final Kg.	N Food Urine Perspiration Feces Balance	CaO Food Urine Feces Balance	P_2O_5 Food Urine Feces Balance	Exercise taken
I Age 14 years, 3 mo.	36.360 36.335	12.357 10.040 0.673 1.177 +0.467	0.823 0.251 0.291 +0.281	2.203 1.220 0.436 +0.547	Walking period
	36.335 36.990	14.600 11.094 0.217* 1.800 +1.650	0.911 0.250 0.507 +0.154	2.669 1.439 0.719 +0.511	Normal activity
II Age 13 years, 10 mo.	43.005 41.740	12.469 12.162 0.386 0.811 −0.879	0.829 0.121 0.202 +0.506	2.224 1.681 0.376 +0.167	Walking period
	41.740 42.640	15.507 12.908 0.133* 1.216 +1.250	0.953 0.215 0.336 +0.402	2.826 1.788 0.560 +0.478	Normal activity

*Estimated.

Summary. From all of these data we conclude that the usual phosphorus requirement of an adult human being of average weight is about 1.5-1.75 gm. P or 3.4-4.0 gm. P_2O_5; that under special conditions of diet and previous feeding this amount may be reduced to about 0.9 gm. P or 2.00 gm. P_2O_5.

Regarding the optimum phosphorus content of the food for immature human beings beyond the age of infancy we have only the above work of Herbst.

PHOSPHORUS REQUIREMENTS OF INFANTS

Very few balance experiments with normal infants are to be found in the literature of the subject from which it is possible to compute their phosphorus requirements. Those which have come to our attention are here recorded in brief.

Michel (1896) conducted balance experiments with new-born infants on a milk diet. A part of the data are as follows:

AVERAGE DAILY RETENTION OF NITROGEN, CALCIUM AND PHOSPHORUS WITH NEW-BORN INFANTS ON A MILK DIET

Age in days	Weight, initial and final Grams	Milk received per day Grams	Milk per kg. body weight	N Gain per kg. body weight	P_2O_5 Gain per kg. body weight	CaO Gain per kg. body weight
5–8	3730 3810	480	127.3	0.312	0.068	0.055
11–14	4400 4520	835	187.2	0.358	0.063	0.045
5–9	2680 2836	485	176.0	0.402	0.062	0.047
7–13	3500 3675	666	185.0	0.302	0.059	0.054
Average.....	3643	617	168.9	0.3435	0.063	0.050

Michel and Perret (1899) report that a two-and-a-half-months-old infant, weighing 4725 gm. at the beginning, gained 19 gm. per day for 3 days on a daily intake of 1.675 gm. nitrogen, 0.268 gm. P_2O_5 and 0.377 gm. CaO, which equals 0.35 gm. nitrogen, 0.056 gm. P_2O_5 and 0.079 gm. CaO per kg. body weight. The storage of nitrogen was 0.785 gm., and of P_2O_5 0.121 gm. per day.

Blauberg (1900a, 1900b) compared artificial with natural feeding of infants. Balance data for calcium, magnesium, and phosphorus are as follows:

DAILY CALCIUM, MAGNESIUM AND PHOSPHORUS BALANCES WITH ARTIFICIALLY FED INFANTS—Grams

Subject	Diet	Income CaO	Balance CaO	Income MgO	Balance MgO	Income P_2O_5	Balance P_2O_5
1 Atrophic.....	Diluted, sweetened and sterilized cow's milk..	.752	0.154	.102	0.032	.725	0.149
2 Atrophic.....	"Kufeke mehl" and water....	.096	—0.052	.095	—0.027	.465	—0.054
3 Normal (?) 6½ mo. old...	Sterilized, undiluted cow's milk.....	1.784	0.924	.129	0.017	1.766	0.507
4 Normal 5 mo. old.....	Mother's milk	.272	0.018	.044	0.018	0.203	0.093

From these data the author concludes that we must consider feeding with cow's milk, even when diluted, to be "supernutrition" as regards the above mineral nutrients, that is, considering the healthy breast-fed infant as the standard.

In Keller's experiments (1900b) with infants on milk diet (see table on p. 452) it was found that on human milk satisfactory gain in weight and retention of nitrogen and phosphorus were induced in infants 2-5 months old (Exp. 2, 6 and 8), weighing 3300 to 4350 gm., on an intake of 1.512-1.875 gm. N and 0.268-0.325 gm. P_2O_5 daily, which is equivalent to 361-485 mg. N and 67-81 mg. P_2O_5, or 29-35 mg. P, per kilogram of body weight.

In these experiments satisfactory gain in weight was not produced with diluted cow's milk. A maximum gain in weight was produced with whole cow's milk, however, containing much more than the above-mentioned amounts of nitrogen and phosphorus, with a 10-months-old child.

From Netter's data (1900) we compute that 6 healthy infants, with an average age of 8.8 months, made the following average daily gains per kilo of body weight on intake per kilo as stated: Intake of milk 144 c.c., of CaO 0.261 gm., and of P_2O_5 0.335 gm.; gain of nitrogen 0.204 gm., CaO 0.059 gm., and of P_2O_5 0.061 gm.

Rothschild and Netter (1901) studied the effect of variation in the amount of milk taken by infants on the thoroughness of its utilization. Children from 4-10 months old were given milk in amounts varying from 125.5-190.2 gm. per kg. of body weight. The greatest gain of nitrogen and phosphorus per day, per kg. of body weight, occurred with a child 8 months old, weighing 7270 gm., and receiving 177.2 gm. of milk per kg. of body weight daily. On this intake the child gained 0.199 gm. nitrogen, 0.095 gm. CaO, and 0.09 gm. P_2O_5 per day, per kg. of body weight. The composition of the milk was not given.

E. Müller (1902) reported experiments with infants 4 and 6 months old comparing the utilization of the constituents of raw and sterilized milk by means of 2 complete balance experiments, each of 7 days' duration, excreta being collected for the last 4 days of each period. The nitrogen and fat of the sterilized milk were better used than of the raw milk. As to calcium and phosphorus the results are inconclusive. A portion of the figures follow.

AVERAGE DAILY BALANCES OF NITROGEN, CALCIUM AND PHOSPHORUS PER KILOGRAM OF BODY WEIGHT WITH INFANTS ON RAW AND STERILE MILK—Grams

Length of period in days	Treatment of milk	N	P_2O_5	CaO
		Food Urine Feces Balance	Food Urine Feces Balance	Food Urine Feces Balance
4	Raw	0.592 0.403 0.117 +0.072	0.272 0.141 0.116 +0.015	0.193 0.002 0.166 +0.025
4	Sterile	0.593 0.357 0.137 +0.099	0.273 0.092 0.149 +0.032	0.193 0.002 0.181 +0.010
4	Raw	0.539 0.424 0.068 +0.047	0.256 0.156 0.047 +0.053	0.195 0.003 0.133 +0.059
4	Sterile	0.540 0.419 0.067 +0.054	0.256 0.151 0.060 +0.045	0.195 0.003 0.133 +0.059

Bruck (1908) has given us two balance experiments with artificially-fed infants. The calcium and phosphorus figures we have calculated from the author's data.

AVERAGE DAILY CALCIUM AND PHOSPHORUS BALANCES WITH ARTIFICIALLY FED INFANTS—Grams

Exp. No.	Age	Initial body weight	CaO intake	CaO retention	Percent CaO retention	P_2O_5 intake	P_2O_5 retention	Percent P_2O_5 retention	Duration of period
1	3 mo.	3400	0.602	0.298	45.3	0.720	0.168	23.5	4 days
2	8½ mo.	5600	0.743	0.299	40.3	1.454	0.300	26.3	3 days

Thus with intakes of 0.212 and 0.260 gm. P_2O_5 per kg. of body weight there was retention of 23.5 and 26.3 percents of these amounts.

During these tests these two infants gained in weight 40 grams and 80 grams respectively; the diet was milk, gruel and malt.

L. F. Meyer (1908) made a study of mineral metabolism in infants as affected by limited intake of food, by increase in the casein of the food, and by increase of the fat of the food. Two infants were the subjects of these experiments. "A" was 3 months old, and "B" was 10 months old at the beginning of the study. Both were in a normal state of general metabolism, though "A" had a slight umbilical hernia, and "B" had exzema, and during the interim between the low diet and the increased food periods suffered from bronchitis. A part of the numerical data are as follows:

AVERAGE DAILY NITROGEN, CALCIUM AND PHOSPHORUS BALANCES WITH NORMAL INFANTS ON MILK DIETS OF VARYING COMPOSITION—Grams

Subject and age	Length of period in days	Diet	N Intake Urine Feces Balance	CaO Intake Urine Feces Balance	P_2O_5 Intake Urine Feces Balance
A 3 months old at beginning	6	Low diet: 200 gm. milk, 800 gm. oat gruel, 20 gm. sugar=44 cal. per kg.	1.056 0.88496 0.1740 −0.00296	0.3485 0.0242 0.2657 +0.0586	0.5686 0.4003 0.2772 −0.1089
"	3	High protein: 2211 gm. of 1:5 milk, 49 gm. casein	3.5515 1.799 0.2556 +1.4969	0.3336 0.0051 0.2911 +0.0374	0.7851 0.4327 0.1668 +0.1856
"	4	High protein and fat: 2927 gm. of 1:5 milk, 80 gm. salt-free butter, 66 gm. casein	3.6296 1.9737 0.202 +1.4539	0.2195 0.0034 0.0226 +0.1935	0.5823 0.3634 0.1042 +0.1147
"	3	High fat diet: 2201 gm. of 1:5 milk, 60 gm. salt-free butter, 66 gm. casein	3.5157 1.7505 0.2171 +1.5481		
B 10 months old at beginning	3	Control: 1500 gm. of 2:3 milk, 1:3 oat gruel, 60 gm. sugar=100 cal. per kg.	5.124 3.3192 0.4439 +1.3609	1.3944 Traces 1.2674 +0.1270	2.0887 0.9649 0.6049 +0.5200
"	8	Low diet: 300 gm. milk, 500 gm. oat gruel, 700 c.c. water, 60 gm. sugar=50 cal. per kg.	2.5690 3.3603 0.2232 −0.0145	0.4809 0.0030 0.4280 +0.0499	0.6695 0.4451 0.2306 −0.0062
"	3	High protein: 4500 gm. of 1:5 milk, 63 gm. casein	4.7732 2.947 0.177 +1.6492	0.5693 0.6273 −0.0580	1.1047 0.5101 0.5027 +0.0919
"	4	High protein and fat: 6000 gm. of 1:5 milk, 100 gm. salt-free butter, 84 gm. casein	4.7732 3.3439 0.214 +1.2153	0.4270 0.5468 −0.1198	0.8285 0.5220 0.4162 −0.1097
"	3	High fat diet: 4500 gm. of 1:5 milk, 75 gm. salt-free butter, 65 gm. casein	4.7732 3.4137 0.1815 +1.1780	0.5693 0.6862 −0.1169	1.1180 0.6483 0.4452 +0.0245

Among the author's conclusions are the following:

While losing in weight, on a deficient diet, a child loses mineral matter and nitrogen; after readjustment to the same diet, so that there is but slight loss in weight, the loss in these constituents may be reduced to zero.

Birk's experiments (1909) (see Rachitis), with two normal infants, showed that with 1.55 and 1.51 grams of phosphorus in the food per day there resulted a retention of 21 and 18 percents of these amounts.

Tobler and Noll (1910) published mineral balances with a healthy infant two and a half months old. The following table sets forth the more important results.

AVERAGE DAILY MINERAL METABOLISM WITH A HEALTHY BREAST-FED INFANT TWO AND ONE HALF MONTHS OLD—Grams

	Intake	Urine	Feces	Balance	Percent retained	Retention per day an kilo.
K_2O	0.3432	0.1124	0.0582	+0.1726	50.27	0.0431
Na_2O	0.2214	0.0078	0.0085	+0.2051	92.64	0.0513
CaO	0.2390	0.0372	0.1485	+0.0533	22.30	0.0133
MgO	0.0284	0.0184				
P_2O_5	0.2102	0.0571	0.0343	+0.1188	56.51	0.0297

The milk contained in 100 gm.: ash 0.1596, K_2O 0.048, Na_2O 0.0309, CaO 0.0334 and P_2O_5 0.0294 gm.; length of experiment 6 days; initial weight 4000 gm.; final weight 4170 grams. From these data we conclude that there was marked retention of phosphorus on an intake of 0.051 gm. P_2O_5, or 0.022 gm. P per kg. of body weight.

Schabad (1910d) reported the following figures for phosphorus excretion by children, which amounts, in relation to food requirements, should, of course, be considered as below the minimum.

AVERAGE DAILY PHOSPHORUS EXCRETION OF HEALTHY CHILDREN ON VARIOUS DIETS

	Total output of P_2O_5 per kilo. per day		P_2O_5 in urine per kilo. per day	Partition of P_2O_5 output	
	Grams	Percent	Grams	Urine Percent	Feces Percent
Naturally nourished children					
New-born	0.0134	17	0.0074	55.6	44.4
2-3 months old	0.0303	40	0.0175	57.3	42.7
4-5 months old	0.0229	65	0.0185	80.6	19.4
Artificially fed children					
3-6 months old	0.214		0.119	57.5	42.5
	.....		.....	65.2	34.8
Older children on bread and milk					
4-5 years	0.159		0.102	64.4	35.6

Summary. New-born infants (Michel) weighing on an average 3643 grams, and receiving of milk 617 gm. per day, or 168.9 gm. per kilogram of body weight, retain about 0.063 gm. P_2O_5, or 0.0275 gm. P, per day; the infant receiving cow's milk may retain considerably more calcium and phosphorus than the breast-fed baby (Blauberg); on human milk infants 2-5 months old made satisfactory retention of phosphorus on an intake of 29-35 mg. per kg. of body weight per day (Keller); infants with an average age of 8-9 months retained

0.061 gm. P_2O_5, or 0.027 gm. P, on an intake of 0.335 gm. P_2O_5, or 0.146 gm. P (Netter); with infants 4-6 months old on artificial feeding there was a retention of 0.015-0.053 gm. P_2O_5, or 0.0065-0.023 gm. P, on an intake of 0.256-0.273 gm. P_2O_5, or 0.112-0.119 gm. P, per day (Müller); with infants 3 and 8½ months of age, and intakes of 0.212 and 0.260 gm. P_2O_5, or 0.093-0.114 gm. P, per kg. of body weight, there was retention of 23.5 and 26.3 percents of these amounts (Bruck); the breast-fed infant may retain 56.5 percent of an intake of 0.051 gm. P_2O_5, or 0.022 gm. P, per kg. of body weight per day (Tobler and Noll). See also Lehmus (1878).

PHOSPHORUS REQUIREMENTS OF CATTLE

Weiske (1873) studied the metabolism of calcium phosphate with two 5-6-months-old calves. One calf retained about a half of the 12 grams of calcium phosphate added to the ration per day, while the other did not retain any of the added calcium phosphate, the difference in results apparently being due to the greater consumption of the basal ration by the latter calf, the food furnishing the entire calcium and phosphorus requirement. Weiske considered that 16.85 gm. CaO and 21.88 gm. P_2O_5 probably represents the full daily requirement of the calves for these elements.

F. Soxhlet (1878), experimenting with 3 young calves on a milk diet, determined the average daily storage per kilogram of live weight of the several mineral constituents as follows:

DAILY MINERAL RETENTION PER KILOGRAM OF LIVE WEIGHT OF THE CALF RECEIVING MILK ALONE

Ash	0.657 gm.	53 percent of the food
P_2O_5	0.274 gm.	72.5 percent of the food
Cl	0.051 gm.	3.8 percent of the food
CaO	0.286 gm.	97.0 percent of the food
MgO	0.008 gm.	30.5 percent of the food
K_2O	0.065 gm.	20.7 percent of the food
Na_2O	0.027 gm.	29.1 percent of the food
Fe_2O_3	0.0008 gm.	38.1 percent of the food

J. Neumann (1893b, 1894) found that a calf weighing 65.63 kg., when fed on milk alone, stored both calcium and phosphorus rapidly. On a daily allowance of 15000 gm. skim milk, and an intake of 24.63 gm. CaO, the calf retained 11.77 gm. CaO. The intake of P_2O_5 was 30.46 gm., and the retention 15.55 gm.

We are not able to present figures of any great value as indicating the phosphorus requirements of milch cows. On account of the nature of the case especial value would attach to observations covering the whole period of pregnancy and lactation.

Anger (1898) made a study of mineral metabolism in milch cows. The cows were fed the following basal ration: 50 kg. fodder beets, 6 kg. straw, 12 kg. hay per 1000 kg. live weight, and in

addition a supplementary allowance of grain, mill feed, or commercial concentrate, the amounts of the supplements being so adjusted as to furnish the same weight of protein in each case.

Anger concludes from this work that the customary assumption that ordinary foods contain as much mineral nutriment as is needed is not justified. The intake and outgo of calcium and phosphorus are in the following table.

CALCIUM AND PHOSPHORUS BALANCES WITH MILCH COWS

Rations Varied from Period to Period—Grams

Cow No.	Week of lactation	Milk produced daily Kg.	CaO			P_2O_5		
			Intake	Outgo	Balance	Intake	Outgo	Balance
1	20	9.53	39.05	45.38	−6.33	66.44	47.46	+18.98
1	22	12.05	41.64	52.88	−11.24	78.72	79.11	−0.39
1	26	10.54	55.78	51.31	+4.47	185.25	143.45	+41.80
1		8.07	41.86	51.57	−9.71	52.24	92.34	−40.10
1	34	6.19	49.81	50.20	−0.39	59.84	52.88	+6.96
1	38	4.71	62.51	49.80	+12.71	97.27	98.88	−1.61
1	41	3.11	99.07	95.33	+3.74	99.20	95.25	+3.95
1	44	2.82	52.57	49.34	+3.23	76.49	68.25	+8.24
2	41	8.12	39.65	52.92	−13.27	48.35	42.25	+6.10
2	43	7.81	62.32	45.66	+16.66	95.91	84.09	+11.82
2	47	5.92	95.27	91.28	+3.99	92.19	85.57	+6.62
2	51	3.91	40.40	36.10	+4.30	65.90	73.90	−8.00
2	55	1.32	33.01	26.58	+6.43	54.94	65.42	−10.48
2	5	15.48	37.16	67.63	−30.47	61.11	85.32	−24.21
3	17	11.32	24.75	30.90	−6.15	63.70	52.81	+10.89
3	20	10.00	40.76	54.17	+13.41	155.32	144.13	+11.19
3	23	9.16	33.36	48.86	−15.50	47.14	78.03	−30.86
4	49	8.17	53.98	52.33	+1.65	90.41	88.66	+1.75
4	56	7.84	55.13	54.91	+0.22	90.13	87.66	+2.47
5	19	13.85	54.90	71.89	−16.99	78.90	93.59	−14.69
5	23	11.43	57.46	60.95	−3.49	57.86	68.91	−11.05
5	26	12.62	58.19	52.14	+6.05	80.70	77.23	+3.47

Note: There was in each period a gain in live weight.

From the work of Jordan, Hart and Patten (1906) we take the following data which have a bearing on the phosphorus requirement of milch cows.

AVERAGE DAILY PHOSPHORUS REQUIREMENT OF MILCH COWS

Weight of cow Lbs.	Daily milk produced Kilos	Phosphorus fed daily Grams	Phosphorus stored daily Grams	Rations
1100	12.813	78.7	8.1	Oat straw 10 lbs., wheat bran 10 lbs., hominy feed 5 lbs., wheat gluten 1 lb.
"	12.027	83.3	12.9	
966	16.715	37.0	17.6	Oat straw 10 lbs., washed bran 10 lbs., corn germ meal 6 lbs., rice meal 3 lbs.
"	16.768	37.0	17.7	
"	14.606	77.0	11.6	Oat straw 10 lbs., wheat bran 10 lbs., rice meal 7 lbs., wheat gluten 2 lbs.

In their study of the metabolism of the ash constituents of wheat bran Hart, McCollum and Humphrey have recorded balance data on high- and low-phosphorus rations with milch cows. These

rations furnished decidedly more or decidedly less phosphorus than the cow requires, and so do not make possible a close estimate of their necessities.

DAILY PHOSPHORUS BALANCES WITH COWS ON HIGH AND LOW PHOSPHORUS RATIONS—Grams

Date	Ration	Intake P_2O_5	Milk P_2O_5	Total outgo P_2O_5	Balance P_2O_5
Dec. 1-4	High phosphorus	190.5	30.4	181.5	+9.0
Dec. 19-22	Low "	46.7	27.6	67.6	−20.9
Dec. 27-28	High "	190.5	27.6	175.2	+15.3
Jan. 6-9	Low "	47.7	23.4	60.3	−12.6
Jan. 18-19	High "	190.5	23.5	155 0	+35.5
Jan. 28-31	Low "	41.5	24.1	55.4	−13.9
Feb. 5	High "	190.5	24.7	65.6	+124.9
Feb. 10-13	Low "	46.7	26.4	58.0	−11.3

Gouin and Andouard (1907) state that if the ration of the calf does not contain legumes and milk it is desirable to add 100 gm. of powdered bone to the daily ration of a calf of 150 kilograms live weight.

Khuen (1908) determined in a 7-day period that with a cow weighing 429.1 kg. and producing, on the average, 7014.3 gm. milk per day, an intake of 61.88 gm. CaO, 44.04 gm. MgO and 84.76 gm. P_2O_5 resulted in a loss of 18.24 gm. CaO, a gain of 0.21 gm. MgO and a loss of 1.76 gm. P_2O_5. The milk contained 16.31 gm. CaO, 1.97 gm. MgO and 54.60 gm. P_2O_5.

From these data we compute that in addition to the amount of phosphorus in the milk a cow must receive more than 70 mg. P_2O_5 per kg. live weight.

Henneberg (Beiträge zur Begründung usw., 2 heft, 1864 S. 53.) determined the maintenance requirement of the steer, for calcium and phosphorus, per 100 kg. live weight, as 100 gm. lime and 50 gm. phosphoric acid. Kellner (1907), in computing the requirements of the milch cow, adds to these figures three times the lime and phosphoric acid content of the 20 kg. of milk produced per 1000 kg. of live weight by milch cows, and so obtains as a total 200 gm. of lime and 140 gm. of phosphoric acid as the requirements of milch cows per 1000 kg. live weight.

A. R. Rose (1912a) concludes that the phosphorus maintenance requirement of a milch cow is the amount of phosphorus eliminated in the milk plus 26 milligrams (P) per kilogram of body weight.

Kellner (1907) computes the calcium and phosphorus retention of the growing calf as 21 gm. CaO and 19 gm. P_2O_5 per day during the first year, and states that the food should contain 40-60 gm. of each.

PHOSPHORUS REQUIREMENTS OF HORSES

There is in existence but very little evidence of value on the phosphorus requirements of horses, especially on the optimum amounts under the various conditions of growth. At the same time it is surely true that there is no other animal in which the development and character of the skeletal tissues contributes in so prominent a way to the economic value.

As is true with other herbivora, little is to be learned from the quantitative estimation of urinary phosphorus, except in connection with the other factors of a complete balance determination. A few data on the amounts of phosphorus in the urine of horses, however, are perhaps worthy of record.

Salkowski (1885 and 1904) found the urinary phosphorus of a horse to be about 0.0107 gm. P_2O_5 per 100 c.c., and 0.2199 gm. in 24 hours.

F. Smith (1889) found in horse urine sometimes only a trace of phosphorus; at others from 0.13 to 9.45 gm. P_2O_5 for 24 hours, an average amount for rest being 1.3 gm., and for work 1.897 gm. P_2O_5.

Liebermann (1891c) found the phosphorus content of the urine of 8 stallions to vary between 0.004 and 0.021 percent P_2O_5, and the 24-hour outgo of P_2O_5 in the urine of six stallions to vary from 0.118 to 0.481 gm.

Tangl (1901) reported balance experiments on mature horses with calcium-deficient rations, an abstract of the report of which we have seen in Maly's Jahresbericht. The original work contains nitrogen, calcium, magnesium and phosphorus balances. The abstract referred to contains little significant material. Tangl states the opinion that the mature horse is able to supply its calcium needs from the same low-calcium fodder, which, with cattle, may produce malnutrition of the bones.

Tangl (1902a, 1902b) studied mineral metabolism in growing horses, with rations of low calcium content. Two horses were used in these experiments. In the first experiment they received hay alone; in the second oats and hay. (See table on p. 423).

The length of the first experiment was 8 days; of the second 6 days. The percentage composition of the foods is as follows:

	Experiment I	Experiment II	
	Hay	Hay	Oats
N	1.366	1.844	2.272
P	0.146	0.165	0.406
Ca	0.440	0.410	0.143
Mg	0.137	0.209	0.104

AVERAGE DAILY NITROGEN, CALCIUM, MAGNESIUM AND PHOSPHORUS BALANCES WITH HORSES ON LOW CALCIUM RATIONS—Grams

Subject No.	Weights Initial Final Ave. daily change Kg.	N Food Urine Feces Balance	Ca Food Urine Feces Balance	Mg Food Urine Feces Balance	P Food Urine Feces Balance	Rations
1	408.0 404.0 −0.50	109.28 70.39 50.70 −11.81	36.38 14.38 21.31 +0.69	11.23 3.43 7.80 +0.09	11.740 0.061 11.830 −0.151	8 kg. hay, 19.6 kg. water
2	445 440 −0.63	109.28 68.11 52.91 −11.74	36.72 14.11 21.84 +0.77	11.33 3.46 7.85 +0.02	11.74 0.13 11.85 −0.24	8 kg. hay, 26.5 kg. water
1	403.8 406.5 +0.45	183.08 102.16 48.30 +32.62	27.23 8.10 17.23 +1.90	14.86 3.44 10.09 +0.33	24.50 0.79 23.07 +0.64	5 kg. hay, 4 kg. oats, 17.3 kg. water
2	432.5 436.8 +0.72	183.08 90.65 53.45 +38.98	27.44 7.69 18.66 +1.09	14.92 3.59 10.70 +0.63	24.50 0.47 23.50 +.053	5 kg. hay, 4 kg. oats, 22.0 kg. water

The drinking water contained 0.0049 percent Ca and 0.0013 percent Mg.

From these data we compute that 0.27 gm. N in hay, per kg. body weight, is below the maintenance requirement, while 0.45 gm., in hay and oats, results in marked storage; the phosphorus content of the hay ration limited calcium storage, since with increased phosphorus but decreased calcium intake, in the second experiment, there was increased calcium storage; with an intake of 0.063 gm. Ca per kg. live weight there was Ca storage; with an intake of 0.029 gm. P per kg. there was loss of P, while with an intake of 0.056 gm. P per kg. there was storage of this element.

Alquier (1905-6) determined that a working horse of 400-450 kilograms (880-990 lbs.) weight requires the equivalent of about 35 grams daily of P_2O_5 for maintenance of phosphorus equilibrium. By the use of a suitable amount of feeding molasses, however, it was found that 25.5 grams of P_2O_5 sufficed for the maintenance of equilibrium, the increased usefulness of the phosphorus being considered to be due to increased solubility, and therefore assimilability, being caused by the action of the sodium and potassium salts occurring abundantly in the molasses.

PHOSPHORUS REQUIREMENTS OF SWINE

From the composition of a year's growth of a pig Kellner (1907) computes, allowing three times as much in the food as the animal will store in the body, that the daily requirement of a pig is 12 gm. each of lime and phosphoric acid.

Hart, McCollum and Fuller (1909) expressed the opinion that the daily phosphorus supply for a 50-lb. growing pig should be at least 3 gm., and that a supply of 4 to 5 gm. is probably a safer quantity. From their experiments with low-phosphorus rations containing 1.12 gm. of phosphorus per kilogram of feed, and from the experiments of Forbes and associates (1914) with similar rations containing 0.92-0.98 gm. of phosphorus per kilogram of feed it appears to be impossible to keep pigs alive indefinitely on food so poor in phosphorus. Doubt attaches to this conclusion, however, because of the fact that these rations were also very low in calcium.

In the course of his investigation of nuclein metabolism in swine Schittenhelm (1910) conducted balance experiments which indicated phosphorus requirements. A part of his figures are as follows:

AVERAGE DAILY NITROGEN AND PHOSPHORUS BALANCES WITH A YOUNG PIG—Grams

Period	Duration in days	N Food Urine Feces Balance	P_2O_5 Food Urine Feces Balance	Ration
1	5	8.70 5.84 0.265 +2.595	3.80 1.20 0.39 +2.21	1500 c. c. milk
2	3	9.49 6.57 0.682 +2.238	4.40 1.63 0.695 +2.075	1500 c. c. milk. 20 gm. yeast nucleinic acid
3	3	8.70 6.30 0.193 +2.207	3.80 1.23 0 191 +2.379	1500 c. c. milk
1	5	14.07 5.20 0.55 +8.32	5.30 1.07 0.45 +3.78	1500 c. c. milk, 300 gm. wheat flour
2	5	16.12 6.38 0.21 +9.52	7.65 3.32 0.20 +4.13	1500 c. c. milk, 300 gm. wheat flour, 14 gm. yeast nucleinic acid
3	5	14.07 6.40 0.295 +7.375	5.30 .... 0.31	1500 c. c. milk, 300 gm. wheat flour

In the first experiment the pig weighed about 15 kg. and is said not to have gained in weight; it was 8 weeks old; in the second experiment the same pig was used, at an age of 4 months. The initial weight was 25.4 kg., and the final weight 31.6 kg. In both experiments there was a large storage of nitrogen and phosphorus. The energy value of the ration in the first experiment was deficient. In the second experiment the increase in weight was 413 gm. daily, with an intake of about 0.5 gm. nitrogen, and 0.2 gm. P_2O_5 per kg. of body weight.

In balance experiments on young swine Weiser (1912) showed that calcium is the limiting factor in the storage of phosphorus on a ration of corn alone. By the addition of calcium carbonate to the corn ration the phosphorus balance changed from negative to positive. It seems certain, therefore, that cereal foods generally, at least corn and barley, contain enough phosphorus to make storage possible if the calcium is increased to an adequate amount. If, however, the protein were increased to such an amount as would provide for maximum growth, by the addition of a more highly nitrogenous food, it may be that the phosphorus of the ration would then limit production, this depending in large measure on the phosphorus content of the proteid supplement. On rations of corn alone Weiser got negative phosphorus balances on intakes of 0.057, 0.050, and 0.049 gm. phosphorus per kg. live weight, and marked storage on an intake of 0.048, 0.060, and 0.051 gm. phosphorus per kg. live weight on barley and starch, or on corn and calcium carbonate, or barley and calcium carbonate.

From the experiments of Forbes, Beegle, Fritz and Mensching (table p. 378) it would appear that actual phosphorus requirements of growing swine are satisfied by corn and the supplementary foods ordinarily fed with corn, but the optimum allowance of phosphorus has not been determined. In these experiments phosphorus was retained on an intake of 48 mg. per kg. of live weight.

PHOSPHORUS REQUIREMENTS OF SHEEP

No very satisfactory data on this subject have come to hand. Weiske (1880) found that a ration of meadow hay and peas contained enough of each of the mineral nutrients to provide for liberal storage at all stages of maturity.

Jordan (1885-6) found that timothy hay and cottonseed meal would sustain large retention of phosphorus, while timothy hay and corn led to moderate retention of phosphorus by a mature wether. On the following page are data from this test.

AVERAGE DAILY PHOSPHORUS AND NITROGEN BALANCES WITH A MATURE WETHER ON NORMAL FOODS—Grams

Nitrogen				Phosphorus				Rations
Food	Urine	Feces	Balance	Food	Urine	Feces	Balance	
20.72	16.78	5.36	−1.42	8.08	0.00	7.48	+0.60	Timothy hay 600 gm.; cottonseed meal 200 gm.
9.02	4.59	4.12	+0.31	2.72	0.00	2.48	+0.24	Timothy hay 600 gm.; corn meal 200 gm.

The first period was of five days duration and the second of four days. No phosphorus was found in the urine.

The following figures from Weiske's work with sheep (copied from Wolff) are of some value as indicating mineral requirement.

DAILY RETENTION OF MINERAL MATTER BY SHEEP—Grams

Age of sheep Months	Live weight Lbs.	Potash	Soda	Lime	Magnesia	Phosphoric acid
5-6	51	2.04	0.84	1.56	0.12	1.09
7-9	66	2.89	1.05	2.00	0.32	1.65
10-12	77	3.05	0.81	1.81	0.38	2.50
13-15	85	2.65	0.72	2.07	0.35	3.14

As to how many times these amounts of the mineral nutrients the food should contain, however, we are unable to say with assurance. Wolff states that the food of young animals reared artificially should contain 2 to 3 times as much lime and phosphoric acid as that actually required as nutriment by the animals.

Kellner (1907) computes, on the basis of Weiske's experiments with lambs 4-5 months old, that the daily retention per 50 kg. of live weight is 2.5-3.8 gm. of lime and 2.0-4.1 gm. of phosphoric acid. Then, allowing 2-3 times these quantities in the food, he recommends 22 gm. of lime and 25 gm. of phosphoric acid per 100 kg. live weight per day.

PHOSPHORUS REQUIREMENTS OF DOGS

In investigations by Forster (1873a), with dogs on low-ash experimental rations, one dog weighing about 24 kg. was in phosphorus equilibrium on about 0.04 gm. P_2O_5, or 0.017 gm. P, per kg. body weight, daily. This may be considered as a minimum figure for artificial conditions.

Munk (1894) showed that a mature dog weighing normally 17.16 kg. lost, per day, during fasting, 4.68 gm. nitrogen and 0.98 gm. P_2O_5 in the urine, and 0.158 gm. nitrogen and 0.187 gm. P_2O_5 in the

feces, a total therefore of 4.838 gm. nitrogen and 1.167 gm. P_2O_5 per day, and 0.0282 gm. nitrogen and 0.068 gm. P_2O_5, or 0.030 gm. P, per kg. per day.

In metabolism studies by Zadik (1899), with dogs, there was, during the 5th period, very nearly a condition of phosphorus equilibrium. A dog weighing 10706 gm. stored 0.009 gm. phosphorus per day in a 6-day period on a total intake of 0.634 gm. phosphorus per day, or 0.059 gm. per kg. live weight. The phosphorus was present mostly in casein. The nitrogen balance was negative, the average daily loss being 0.37 gm. on an intake of 7.25 gm.

Kornauth (1900), in comparing the utilization of different proteins with dogs, obtained balance figures which show that, when the principal source of the protein is meat, an intake of about 55-60 mg. P, per kilogram of body weight per day, is close to the maintenance requirement.

On a diet of meat, lard, crackers and bone ash, Hawk and Gies (1904) maintained a dog weighing 16.96 kg. for 12 days on an intake of 2.456 gm. of phosphorus per day, with a daily phosphorus balance of +0.045 gm. Of this 2.456 gm. phosphorus, 1.779 gm. was present as bone ash.

With another dog, on the same ration, these authors fed the animal 1.95 gm. phosphorus daily (apparently not 0.195 gm. as stated in the original), of which 1.423 gm. was present as bone ash. The dog weighed 11.85 kg., and the daily phosphorus balance was —0.030 gm.

The apparent phosphorus requirement with these dogs was about 0.140-0.170 gram per kg. live weight, the amount being due in part to the comparatively insoluble form in which most of the phosphorus was fed.

Heubner (1909) determined that the phosphorus retention of the normal growing dog was 0.14 gm. per kilogram of body weight per day.

The lowest amounts of calcium and phosphorus on which storage took place in Biernacki's experiments (1909) were 0.044 gram CaO and 0.248 gram P_2O_5, or 0.108 gm. P, per kg. live weight. The amount of phosphorus stated, however, is considerably above the maintenance requirement.

In an investigation on the use of organic and inorganic phosphates in foods, Lipschütz (1911b) determined that, in a 7-day balance experiment, a dog weighing 2450 gm. at the beginning, and

2700 gm. at the end, with a ration of rice, egg albumin, sugar, palmitin, and a salt mixture, including phosphates, and with a daily phosphorus intake of 0.651 gm., or 0.252 gm. per kg. live weight, the retention was 0.084 gm., or 0.033 gm. per kg. live weight per day.

Kochmann and Petzsch (1911), in their study of calcium metabolism in the dog, made observations on phosphorus metabolism from which it is possible to estimate the phosphorus requirement. The dog in question was mature, and weighed 10300-11040 gm. in the periods in which there was a retention of P_2O_5. In 4 periods of 4-5 days each the P_2O_5 balances, on an intake of 3.671 gm., were +0.308, +0.121, —0.260 and +0.622. With an intake of 2.800 gm. P_2O_5 the phosphorus balance was negative. The phosphorus requirement, therefore, appeared to be about 0.114-0.142 gm. per kg. body weight.

From these data it appears that the fasting loss is about 0.030 gm. per kilogram (Munk); the maintenance requirement on an artificial low-ash diet about 0.017 gm. per kilogram (Forster); the maintenance requirement on a more nearly normal diet, with the phosphorus present mostly in casein, was 0.059 gm. per kilogram (Zadik); with a diet containing meat and bone ash the requirement seemed to be about 0.140-0.170 gm. per kilogram (Hawk and Gies); retention took place on intakes of 0.108 gm. (Biernacki), and 0.252 gm. (Lipschütz), while Heubner showed that the normal retention is about 0.140 gm. per kilogram in a growing dog.

The data are insufficient for the establishment of general conclusions.

PHOSPHORUS REQUIREMENTS OF RATS

From the experiments of Gregersen (1911) we deduce the observations that on a nitrogen-free, phosphorus-free diet the daily elimination of phosphorus per 1000 gm. of body weight is 36.5 milligrams, the eight figures averaged varying from 28 to 54.5 milligrams. From an experiment by McCollum (1909), we compute from a determination with a single individual on a phosphorus-free diet, that the outgo was 35.0 milligrams per 1000 gm. of body weight. The experiments of neither author afford satisfactory evidence for judgment as to the maintenance or growth requirement on normal foods.

PHOSPHORUS METABOLISM AS AFFECTED BY VARIOUS CONDITIONS

EFFECTS OF ALTITUDE ON PHOSPHORUS METABOLISM

Von Wendt (1910) studied metabolism in man at three different altitudes in the Alps. Complete nitrogen and mineral balances were made. A portion of the data are as follows:

DAILY NITROGEN AND MINERAL BALANCES WITH A MAN AT DIFFERENT ALTITUDES IN THE ALPS—Grams

Day	Altitude Meters	N Food	N Urine	N Feces	N Balance	S Food	S Urine	S Feces	S Balance	Fe Food	Fe Urine + Feces	Fe Balance	Ca Food	Ca Urine	Ca Feces	Ca Balance	P Food	P Urine	P Feces	P Balance
1	3000	22.58	13.64	1.42	+7.52	1.706	1.062	0.343	+0.301	0.156	0.101	+0.055	0.160	0.177	0.200	−0.217	0.861	0.661	0.197	+0.003
2	3000	22.58	16.02	1.42	+5.14	1.706	1.343	0.343	+0.020	0.156	0.101	+0.055	0.160	0.197	0.200	−0.237	0.861	0.774	0.197	−0.110
3	3000	22.58	18.23	1.42	+2.93	1.106	0.963	0.343	+0.400	0.156	0.101	+0.055	0.160	0.140	0.200	−0.180	0.861	0.766	0.197	−0.102
4	3000	22.58	15.70	1.42	+5.46	1.706	1.123	0.343	+0.240	0.156	0.101	+0.055	0.160	0.157	0.200	−0.197	0.861	0.828	0.197	−0.164
1	4560	22.58	14.58	1.22	+6.78	1.706	0.892	0.282	+0.532	0.156	0.140	+0.016	0.160	0.193	0.239	−0.272	0.861	0.585	0.184	+0.092
2	4560	22.58	14.38	1.22	+6.98	1.706	0.928	0.282	+0.496	0.156	0.140	+0.016	0.160	0.137	0.239	−0.216	0.861	0.658	0.184	+0.019
3	4560	22.58	15.00	1.22	+6.36	1.706	1.086	0.282	+0.338	0.156	0.140	+0.016	0.160	0.143	0.239	−0.222	0.861	0.555	0.184	+0.012
4	4560	3.30	9.97	1.22	−7.89	0.435	0.672	0.282	−0.519	0.003	0.140	−0.137	0.083	0.124	0.239	−0.280	0.284	0.508	0.184	−0.408
1	3000	22.58	14.25	1.06	+7.27	1.706	0.950	0.331	+0.425	0.156	0.096	+0.060	0.160	0.191	0.216	−0.247	0.861	1.057	0.241	−0.437
2	3000	22.58	15.88	1.06	+5.64	1.706	1.198	0.331	+0.177	0.156	0.096	+0.060	0.160	0.176	0.216	−0.232	0.861	1.140	0.241	−0.520
3	3000	3.30	11.90	1.06	−8.85	0.435	1.112	0.331	−1.008	0.003	0.096	−0.093	0.083	0.145	0.216	−0.278	0.284	0.629	0.241	−0.586

The first and third series of balances were at an altitude of 3000 meters, and the second at 4560 meters. The nitrogen balance was positive at all times, except on the two days of low nitrogen intake. Reckoned as muscle substance, more than 100 gm. per day was formed. The parallel sulphur balances showed that the nitrogen storage was protein synthesis. The phosphorus balance was positive only during the second period, at the higher altitude. Von Wendt believes, from the relative amounts of nitrogen, sulphur, phosphorus and iron stored, that during the first and third periods, at the lower altitude, there was much haemoglobin synthesized, while synthesis of muscle substance predominated during the second period at the higher altitude.

THE INFLUENCE OF AMOUNT OF FOOD ON PHOSPHORUS METABOLISM

The plane of nutrition on which an animal is living, as determined by the nutrients available, naturally involves phosphorus as well as the other essential constituents. Thus Pettenkofer and Voit (1866) showed that on a medium diet the phosphorus in the urine was one-third more than during fast, the subject being at rest in both cases, and Forster (1873a), experimenting with foods poor in mineral matter, showed that the less the quantity of the salt-poor foods ingested the greater was the loss of phosphorus, due to tissue katabolism, from the body. An observation of similar portent was made by Weiske (1894), who found that in the less well-developed rabbits of the same age and kind the bones and also, to a less extent, the teeth, contained subnormal percentages of mineral matter.

Gevaerts (1901), in a study of feeding white rats on phosphorus-free foods, submits data which we have condensed as in the table on p. 431.

From these data we see that in the white rat the phosphorus excretion in the urine from a phosphorus-free diet is very much less in amount than that present in the urine during starvation; and also that on a ration of sucrose and edestin, or on sucrose and ovalbumin, there is much less phosphorus in the urine than on a ration of sucrose alone, the edestin and ovalbumin naturally being more efficient than the sucrose to spare the phosphorus-containing proteins of the body.

Sherman (1902) showed, in experiments with human subjects, that nitrogen, sulphur and phosphorus balances all reflected consistently, by change of sign, the change from restricted to liberal diet, or the reverse. (Exp. 7-10 p. 432.) The diet was crackers, butter and milk. It is elsewhere shown that nitrogen, sulphur and phosphorus balances need not, of necessity, show interdependence in their variations.

AVERAGE DAILY EXCRETION OF PHOSPHORUS IN THE URINE OF WHITE RATS ON PHOSPHORUS-FREE DIETS—Grams

Experiment, period and days	Ration	Initial live weight	Gain or loss in weight	Loss in phosphorus
1 A—3	Sucrose 15 gm.	210	−8.3	0.0093
1 B—3	Sucrose 15 gm.	198	−7.7	0.0141
2 A—2	Sucrose 15 gm.	182	−11.5	0.0060
2 B—3	Sucrose 15 gm., edestin 2 gm.	159	−4.0	0.00085
2 C—1	Sucrose 15 gm.	147	−2.0	0.0050
2 D—1	Sucrose 15 gm., edestin 2 gm.	145	+7.0	0.0033
3 A—2	Sucrose 15 gm.	181	−11.5	0.0060
3 B—3	Sucrose 15 gm., edestin 2 gm.	158	−1.0	0.0010
3 C—3	Sucrose 15 gm.	155	−3.0	0.0040
3 D—1	Sucrose 15 gm., edestin 2 gm	146	+8.0	0.0038
4 A—2	Sucrose 15 gm.	202	−9.5	0.0060
4 B—3	Sucrose 15 gm., edestin 2 gm.	183	−5.0	0.0010
4 C—3	Sucrose 15 gm.	168	−2.7	0.0031
4 D—1	Sucrose 15 gm., edestin 2 gm.	160	+8.0	0.0017
5 A—6	Sucrose 15 gm., edestin 2 gm.	255	−1.7	0.0041
5 B—1	Complete starvation.	180	−27.0	0.0124
5 C—1	Sucrose 15 gm., edestin 2 gm.	153	−1.0	0.0019
5 D—1	Sucrose 15 gm., ovalbumin 2 gm.	152	−4.0	0.0008
5 E—1	Sucrose 15 gm., edestin 2 gm.	148	−1.0	0.0013
5 F—3	Complete starvation.	147	−6.3	
5 G—2	Sucrose 15 gm., edestin 2 gm.	128	0.0	
5 H—2	Sucrose 15 gm., edestin 2 gm.	128	+1.0	0.0018
6 A—1	Complete starvation.	240	−27.0	0.0124
6 B—3	Sucrose 15 gm., edestin 2 gm.	213	−6.0	0.0005
6 C—3	Complete starvation.	195	−5.7	
6 D—2	Sucrose and edestin	178	−2.5	
6 E—2	Sucrose and edestin	173	+4.0	0.0015
7 A—1	Complete starvation.	280	−28.0	0.0124
7 B—3	Sucrose 15 gm., ovalbumin 2 gm.	252	−0.7	0.0029
8 A—1	Sucrose 15 gm.	290	−22.0	0.0072
8 B—2	Sucrose 15 gm., edestin 2 gm.	268	−2.5	0.0036

AVERAGE DAILY NITROGEN, SULPHUR AND PHOSPHORUS BALANCES WITH A MAN ON A DIET OF CRACKERS, BUTTER AND MILK—Grams

Experiment No.	Duration in days	Fuel value Cals.	N Food / Urine / Feces / Balance	S Food / Urine / Feces / Balance	P Food / Urine / Feces / Balance	Food: Crackers	Food: Milk	Food: Butter	Remarks
1	4	2908	15.82 / 14.31 / 0.74 / +0.77	1.12 / 0.95 / 0.06 / +0.11	2.29 / 1.41 / 0.78 / +0.10	300	2040	40	Fore-period
2	4	2901	15.82 / 14.67 / 0.67 / +0.48	1.12 / 0.97 / 0.06 / +0.09	2.29 / 1.48 / 0.73 / +0.08	300	2040	40	Loss of sleep
3	4	2913	15.82 / 14.16 / 0.70 / +0.96	1.12 / 0.93 / 0.06 / +0.13	2.29 / 1.42 / 0.78 / +0.09	300	2040	40	After-period
4	4	2082	12.05 / 10.43 / 0.74 / +0.88	0.94 / 0.72 / 0.09 / +0.13	1.40 / 1.03 / 0.44 / −0.07	405	1000	60	Low protein
5	4	2607	18.52 / 16.50 / 0.87 / +1.15	1.44 / 1.12 / 0.08 / +0.24	3.07 / 1.74 / 1.10 / +0.23	120	3060	0	High protein
6	4	1555	9.76 / 10.94 / 0.27 / −1.45	0.69 / 0.75 / 0.02 / −0.08	1.60 / 1.12 / 0.37 / +0.11	120	1530	0	Intermediate period
7	5	1660	10.11 / 11.51 / 0.45 / −1.85	0.70 / 0.83 / 0.04 / −0.17	1.58 / 1.00 / 0.60 / −0.02	150	1500	0	Food restricted
8	5	3336	20.22 / 15.52 / 1.04 / +3.66	1.40 / 1.06 / 0.09 / +0.25	3.16 / 1.49 / 1.42 / +0.25	300	3000	0	Twice as much as above
9	5	1656	10.11 / 12.87 / 0.43 / −3.19	0.70 / 0.88 / 0.04 / −0.22	1.58 / 1.32 / 0.50 / −0.24	150	1500	0	Food restricted
10	3	3329	20.70 / 16.58 / 1.05 / +3.07	1.36 / 1.21 / 0.10 / +0.05	3.26 / 1.49 / 1.37 / +0.40	300	3000	0	Twice as much as above

Marked loss of sleep for 3 successive nights resulted in a small increase in the excretion of nitrogen, sulphur and phosphorus, the proportions not being markedly abnormal. The increased elimination due to loss of sleep did not appear until the third day, while changes resulting from alteration of the diet were always perceptible on the first day. The elimination of phosphorus by the intestine was large and variable.

Kaufmann and Mohr (1903) studied metabolism during overfeeding, following an extended period of underfeeding, with two adult human beings. Both subjects were in bodily health during this experiment on forced feeding. The average daily nitrogen, phosphorus and calcium storage in grams was as indicated below:

Subject	Days	N		P_2O_5		CaO		Body weight Kg.
		Intake	Retention	Intake	Retention	Intake	Retention	
1	7	18.38	4.90	6.20	1.35	6.07	2.34	62.0
2	10	16.45	5.67	5.36	1.37	4.46	2.10	57.7

The amount of retention is much influenced by the state of impoverishment existing, and the nutriment available.

Hawk (1903) compared phosphorus balance on moderate and excessive protein intake. With the excessive ingestion of protein there was a negative phosphorus balance, while with less protein in the fore- and after-periods there were positive balances. The ingestion of 4.96 gm. per day of phosphorus (stated as P_2O_5) provided for storage of this element in men of 56.2-60 kg. body weight.

In this experiment the sudden marked increase in phosphorus intake coincident with excessive protein ingestion, so greatly increased the urinary phosphorus excretion as to change a positive to a negative balance.

DAILY PHOSPHORUS BALANCES ON ADULT MEN WITH VARYING AMOUNTS OF PROTEIN IN THE FOOD—Grams

Subject	Period	Length of period in days	Food P_2O_5	Urine P_2O_5	Feces P_2O_5	Balance P_2O_5	Rations
H	I	4	4.96	2.58	2.07	+0.32	300 gm. crackers, 60 gm. butter, 1650 gm. milk.
H	II	1	5.82	3.28	3.01	−0.47	225 gm. beef, 250 gm. crackers, 60 gm. butter, 1375 gm. milk
H	III	4	4.96	2.57	1.92	+0.47	300 gm. crackers, 60 gm. butter, 1650 gm. milk.
R	I	4	4.96	3.15	1.52	+0.29	Same as Period I above.
R	II	1	5.82	3.62	3.45	−1.25	Same as Period II above.
R	III	4	4.96	2.78	1.89	+0.29	Same as Period III above.

Initial weight of H—56.2 kg., of R—60 kg.

C. Tigerstedt (1904) reported results on nitrogen and phosphorus balance experiments with a young man 20 years old on rations varying in phosphorus content. Daily balances, as stated by the author, we have computed to average daily balances per period. A part of the results are as follows:

AVERAGE DAILY PHOSPHORUS BALANCES WITH A MAN TWENTY YEARS OLD ON DIETS OF DIFFERENT PHOSPHORUS CONTENT

Grams

Days	Nitrogen	Phosphorus				Daily rations
	Balance	Food	Urine	Feces	Balance	
1	−13.06	0.027	0.649	mean 0.134	−0.756	100 gm. meal, 18 gm. sugar, 207 gm. sago gruel, 3 gm. salt.
2	−7.36	traces	0.730		−0.864	70 gm. sugar, 270 gm. jelly, 120 gm. potato, 80 gm. apple.
3-14	+1.23	2.545	1.333	1.102	+0.200	About 70 gm. butter, 750 c.c. milk, 150 gm. bread,
15-17	−2.43	2.515	1.506	1.291	−0.282	430 gm. potatoes, 150 gm. roast meat, 150 gm. groats.
18-22	+2.91	3.056	1.612	1.253	+0.191	Same as above plus additional milk and a casein preparation, and on days 19-22, 160 gm. zweiback.
23-25	−0.14	1.757	0.956	0.935	−0.134	First two days, 275 gm. groats, 180 gm. rye bread, 100 gm. butter; third day, 200 gm. groats, 140 gm. rye bread, 80 gm. butter.

Weight of subject, 62 kg.

The first two days' rations were very low in both nitrogen and phosphorus. The results of these two days show that the phosphorus arising from the mucous coat of the intestine and from the intestinal juices, which appears in the feces, is about 0.134 gm. daily, but this amount may vary with the amount and kind of food. This phosphorus is less in amount when food is given which is poor in both nitrogen and phosphorus than in starvation, since such foods serve to protect body proteins, etc., from katabolism.

The negative balance on days 15-17 was due principally to imperfect absorption from the intestine.

The last ration was a vegetable dietary, except for the butter. The negative nitrogen balance and the low calcium content of the cereal diet were both unfavorable to phosphorus retention.

From the work of Lüthje and Berger (1904) (see p. 218) we would infer that calcium and phosphorus storage might take place as rapidly in a normal man, who had never been ill, as in a typhus convalescent; but the nitrogen retention seems to be much more marked in the convalescent, in a greatly reduced state, than it is in either the well-nourished convalescent or the normal cases. The maximum phosphorus retention with a convalescent was 2.832 gm. P_2O_5, and in a normal case 3.381 gm. P_2O_5 daily, in each case for 10 days.

Sweet and Levene (1907) made observations on nuclein metabolism in a dog with an Eck fistula which show the same ability of the organism to adapt itself to different planes of nuclein metabolism that has frequently been noted with regard to total nitrogen and phosphorus.

Vozárik (1909) studied the effect of variation in the amount of protein in the diet on the acidity, ammonia, phosphorus and total nitrogen in the urine of children. Increase of protein increased the outgo of all these constituents, both per day and per c.c. of urine.

Biernacki (1909) sought to determine with dogs the effects of "supernutrition" on mineral metabolism. The foods added to the standard diets were butter, sugar and eggs. In each case the animal, though previously storing phosphorus, accomplished an increased storage through the ingestion of excessive amounts of these foodstuffs. Of calcium also there was in each case an increased storage, or decreased loss, when the supplementary foods were given.

The conduct of mineral metabolism experiments on a really satisfactory basis requires that there be intermediate periods of sufficient length to allow the effects of previous feeding to disappear.

Numerical data from this study are below.

DAILY NITROGEN, CALCIUM AND PHOSPHORUS BALANCES WTH DOGS—Grams

Experiment No.	Periods	Change in weight of dog	Nitrogen balance	CaO intake	CaO balance	P_2O_5 intake	P_2O_5 balance	Diet
I	Fore-period 8 days	5700 −250	−0.0264	0.0915	−0.0019	1.4127	+0.3527	Meat; rice
	Fat period 8 days	5459 +170	+0.5232	0.2385	+0.1673	1.7007	+0.8059	Meat; rice; butter
	After-period 8 days	5620 −210	+0.2886	0.0915	+0.0261	1.4127	+0.4547	Meat; rice
II	Fore-period 6 days	5290 +110	+0.8316	0.0927	−0.0328	1.4776	+0.5297	Meat; rice
	Sugar period 6 days	5400 +380	+1.5553	0.0927	−0.0159	1.4776	+0.6736	Meat; rice; sugar
	After-period 6 days	5780 −160	+0.4855	0.0927	−0.0301	1.4776	+0.4845	Meat; rice
III	Fore-period 6 days	5620 −120	−0.1618	0.1289	−0.0090	1.6643	+0.5540	Milk; rice
	Fat period 6 days	5500 +290	+0.6057	0.2737	+0.1147	1.9523	+0.5769	Milk; rice; butter
	After-period 6 days	5790 −50	+0.5142	0.1289	−0.0092	1.6643	+0.2515	Milk; rice
	Protein period 6 days	5740 +130	+1.6857	0.1475	−0.0818	1.5778	+0.6692	Milk; rice; eggs

The increased nitrogen storage resulting from the addition of butter and sugar indicates that these foods were able to replace a portion of the protein previously used for energy production, thus allowing its participation, along with calcium and phosphorus, in synthesis of tissue.

Heubner (1909) conducted an experiment with young dogs to study the effects of phosphorus starvation. He used 6 pups taken at weaning time, when 38 days old, and fed them various rations for 7 weeks, after which a part were killed, and their tissues examined. Two were fed on a low-phosphorus ration composed of egg-white, rice, sugar, palmin, ferric saccharate, and sodium, potassium, calcium and magnesium chlorides.

Three others received a similar ration containing casein from cow's milk, and with a part of the alkali chlorides replaced by diphosphates, so that the food contained one percent more phosphorus than the above. The sixth dog had bread, milk, meat, potato, rice and fat.

The phosphorus-starved dogs were undersized, their bones became curved, and the abnormality of their diet was in many ways outwardly evident. An examination of the bones seemed to show decided differences in appearance from those of cases where calcium starvation was known to prevail.

The feces of these dogs did not contain phosphorus in amounts corresponding with the food; in fact, the phosphorus content of the dry feces was somewhat nearly the same throughout, and apparently not related to the food. The phosphorus content of the urine, however, varied greatly, and in accord with the amount in the food. Data from this work are below.

DATA SHOWING PHOSPHORUS STORAGE IN YOUNG DOGS

No. of dog	Age of dog in weeks	Weight Kg.	Phosphorus in urine Percent	Phosphorus storage per day, per kg. Grams	Nutrition
1	5	1.13	0.38	....	Mother's milk
6	5	1.00	0.51	....	Mother's milk
3	7	1.60	0.029	0.14	Cow's milk
3	10.5	2.80	0.039	(0.026)	Mixed diet
3	17	4.80	0.052	0.037	Mixed diet
1	7	1.32	0.39	0.13	P in excess
1	10.5	1.80	0.17	0.19	P in excess
6	11	2.20	0.17	0.23	P in excess
2	7	1.23	0.0024	0.008	P hunger
2	10.5	1.70	0.001	0.015	P hunger
5	11	1.90	0.0007	0.016	P hunger

Kochmann (1911) studied calcium metabolism, as affected by other food constituents, with three grown dogs fed on dog biscuit and water. Below are his figures on phosphorus balance for Dog III.

Nine out of twelve of the periods were 5 days in length. That 5 days is too short a period for mineral metabolism studies is manifest as we compare periods 2, 3 and 4, the intake being the same, and periods 8-12, the intake in these also being the same.

In the urinary figures there is some evidence of delayed outgo as the intake changed; and in the two series above mentioned the change in balance is due principally to variation in feces phosphorus, the urinary phosphorus remaining much more nearly constant. The change in feces phosphorus, especially its progressive decrease in periods 9, 10, 11 and 12, was not interpreted by the author.

It is of interest to note that with each of the three increases in intake there was a degree of improvement in retention which the animal was unable to sustain, since in the next period after the one in which the intake was increased there was in each case a decreased retention.

AVERAGE DAILY PHOSPHORUS (P_2O_5) METABOLISM OF A DOG RECEIVING VARIOUS AMOUNTS OF FOOD—Grams

Period	Length of period in days	Weight of dog	Intake of dog biscuit	Intake P_2O_5	Urine P_2O_5	Feces P_2O_5	Balance P_2O_5
1	4	6750	100	2.191	1.159	1.326	−0.293
2	5	6600	150	3.286	1.200	1.937	+0.149
3	3	6450	150	3.286	1.243	2.104	−0.061
4	5	6280	150	3.286	1.212	2.262	−0.188
5	5	6260	175	3.833	1.219	2.038	+0.576
6	5	6320	175	3.834	1.305	2.502	+0.027
7	6	6355	200	4.381	1.250	2.251	+0.880
8	5	6420	200	3.994	1.300	2.467	+0.227
9	5	6460	200	3.994	1.078	2.908	+0.012
10	5	6300	200	3.994	1.056	2.815	+0.123
11	5	6350	200	3.994	1.016	2.190	+0.788
12	5	6450	200	3.994	1.085	2.020	+0.889

Summary. Balance experiments show us that increased intake of phosphorus usually causes increased elimination in the urine with carnivora, in the feces with herbivora, and according to the nature of the diet with omnivora, the increased outgo being accompanied by increased retention or production at such times as so determined by the general state of nutrition. Marked increase in intake, incidental to excessive protein ingestion, is sometimes accompanied by decreased retention; but this is not the usual course of metabolism.

During deficient intake of phosphorus, or of food in general, the consumption of phosphorus-free food may decrease the loss of phosphorus, through the protection afforded the body tissues from katabolism.

Even in a normal state of nutrition, grown animals are able to increase their bodily reserves of phosphorus to a considerable extent; and after sickness the retention may be very extensive, though apparently not of a different order from that characteristic of normal growth.

As with other nutrients, the retention of phosphorus is not directly as the intake, but, other conditions being favorable, as the amount of intake in excess of the maintenance requirement. After a certain point is reached, however, the rate of increased retention coincident with increased intake, begins to fall off, and, with indefinitely continued increase of intake, a point is reached where further increase does not lead to further storage, but only to elimination.

Animals have a capacity to adapt their phosphorus exchanges to different planes of metabolism, as with other nutrients, nitrogen in particular.

PHOSPHORUS METABOLISM DURING FAST

In fasting there is a very considerable loss of phosphorus from the body, due to the katabolism of the phosphorus-containing proteins which are consumed for energy production, a much greater loss, naturally, than where foods are used which are poor in phosphorus. In this latter case phosphorus-containing tissues are protected, and a portion of the katabolized phosphorus may be retained and utilized along with nutrients supplied by the food. Considerable attention has also been given the possibility that the bones lose phosphorus during starvation.

I. Munk (1887) announced conclusions reached in the course of fasting experiments with Cetti as follows: In fasting, the phosphorus of the urine is united partly with potassium, and partly with calcium and magnesium. The ratio of phosphorus to nitrogen in the urine is about 1:4.5 during fast, while in the soft parts of the body the ratio is about 1:7. The increase of phosphorus outgo is both absolute and relative to nitrogen. The calcium excretion is 3 or 4 times that amount which would correspond to the break-down of flesh. Magnesium excretion also is much greater than as if derived from the flesh, but during fast the calcium exceeds the magnesium. From these facts he concluded that the bones contribute to the phosphorus loss during starvation.

F. A. Falck (1875), in studying hunger metabolism in a dog, determined that a dog weighing 21210 grams lost in body weight 10380 grams, and in phosphorus 31.7 gm. P_2O_5, equivalent to 5706 gm. fat-free fresh dog-flesh, while starving to death in 61¼ days.

Luciani (1889) made a general physiological study of fasting, with Succi as a subject. In 1889 he reported results from a 30-day fast from which it would appear, in harmony with the conclusions of Munk, that the nitrogen and the phosphorus of the urine have in part an independent origin early in the fasting period, as well as late, but most markedly so after a considerable duration of the fast. A portion of his figures are as follows:

DAILY PHOSPHORUS ELIMINATION IN THE URINE DURING FAST

Day of fast	P Grams	N/P	Day of fast	P Grams	N/P	Day of fast	P Grams	N/P
1	0.842	16.3	11	0.620	12.7	21	0.325	11.9
2	0.898	12.2	12	0.441	16.2	22	0.313	10.2
3	0.920	15.0	13	0.137	25.6	23	0.459	10.4
4	0.925	13.8	14	0.434	12.2	24	0.344	16.1
5	1.031	12.4	15	0.449	11.4	25	0.257	27.4
6	0.932	13.0	16	0.468	11.7	26	0.341	17.7
7	0.814	11.5	17	0.531	11.6	27	0.375	14.3
8	0.691	12.1	18	0.439	12.3	28	0.349	16.0
9	0.593	13.1	19	0.415	12.3	29	0.345	11.8
10	0.544	12.4	20	0.382	11.5	30	0.444	14.9

C. Lehmann, Müller, Munk, Senator and Zuntz (1893) reported on fasting experiments with Cetti, the professional faster, and Breithaupt, a cobbler. Both drank water at will, Cetti took no exercise; Breithaupt assisted in laboratory work.

DAILY NITROGEN AND PHOSPHORUS EXCRETION IN THE URINE BY CETTI AND BREITHAUPT DURING FAST—Grams

Cetti			Breithaupt		
Day of fast	N	P_2O_5	Day of fast	N	P_2O_5
1	13.545	2.597	1	10.01	1.56
2	12.586	2.925	2	9.92	1.89
3	13.121	3.289	3	13.29	2.53
4	12.393	2.974	4	12.78	2.36
5	10.695	2.871	5	10.95	2.19
6	10.100	2.667	6	9.88	2.29
7	10.885	2.663			
8	8.903	1.722			
9	10.833	2.065			
10	9.467	0.948			

The average daily fecal nitrogen and phosphorus (P_2O_5) with Cetti were 0.316 gm. and 0.205 gm., respectively, and with Breithaupt, 0.113 gm. and 0.140 gm., respectively.

The phosphorus of the urine was found to be largely combined with potassium, more than twice as much as was present in combination with calcium and magnesium. Calcium and magnesium were present in the urine only as phosphates. By computation the authors show that it would have been impossible for the flesh to have given up all of the phosphorus excreted. In both cases a part of the phosphorus is shown to have come from the bones.

Gusmitta (1893) studied the composition of the bones of several rabbits and a dog as affected by starvation. The method was amputation of parts, and comparison with others remaining after recovery of the animal from the mutilation, and after subsequent starvation to death.

The bones were shown to lose during starvation, in weight, volume and specific gravity, and to increase in porosity; there was a slight increase in water, and a uniform decrease in all organic and inorganic constituents. The results seem indisputable in showing that starvation causes katabolism of bones as well as soft parts.

The following figures set forth results with the dog experimented upon.

CONSTITUENTS OF BONES OF A DOG AS AFFECTED BY STARVATION

Dry weight of bones	Total inorganic matter		Iron phosphate		Calcium carbonate		Magnesium phosphate		Calcium phosphate	
	Grams	Percent	Grams	Percent	Grams	Percent	Grams	Percent	Grams	Percent
Right cubitus and radius, dog in normal state, 11.917 gm.	7.261	60.93	0.1090*	0.16	0.6888	5.78	0.1120	0.94	6.4208	53.88
Left cubitus and radius, after starvation, 10.382 gm.	6.556	63.16	0.0134	0.13	0.5391	5.20	0.0809	0.78	5.9011	56.84

* Apparently erroneous; 0.0169 would harmonize with percentage figure.

I. Munk (1894) reported a fasting experiment with a dog which shows more clearly still than his previous experiment on Cetti that in inanition a part of the nitrogen, calcium, magnesium and phosphorus loss is from the bones. Some of his figures are as follows:

EXCRETION OF NITROGEN AND PHOSPHORUS BY A MATURE FASTING DOG—Grams

Day	Body weight Kg.	Urine		
		N	P_2O_5	P_2O_5:N
Prelim.	17.16	16.82	1.99	1:8.4
1	16.94	5.59	0.820	1:6.8
2	16.48	5.31	0.901	1:5.9
3	15.86	5.32	0.996	1:5.3
4	15.58	5.28	1.106	1:4.8
5	15.35	5.18	1.268	1:4.1
6	15.16	4.29	0.776	1:5.5
7	14.95	4.66	1.020	1:4.5
8	14.77	3.79	1.210	1:3.1
9	14.49	3.59	0.883	1:4.1
10	14.27	3.74	0.851	1:4.4
Total loss	2.89	46.75	9.83	1:4.8
Average	0.29	4.68	0.98	
		Feces		
Total		1.576	1.874	1:0.84
Average		0.158	0.187	

During the preliminary period of several days the diet was liberal and normal; ratio of P_2O_5:N in urine as 1:8.4. During fast this ratio was 1:4.8. The increased phosphorus in the urine, the author computes, would be equal to that in 32 gm. fresh bone; the extra calcium would imply the destruction of 31.5 gm. fresh bone, and an excess of magnesium was also to be accounted for.

Heymans's (1896) work on metabolism during starvation of the rabbit shows that there is a premortal rise in phosphorus excretion. If the fast is discontinued by the giving of food the phosphorus excretion in the urine is very much less than either the normal or the fasting excretion, until an equilibrium is reëstablished.

Weiske (1897), experimenting with rabbits, studied the effects of starvation on the composition of the bones, teeth and other tissues. Four rabbits from the same litter were used, No. 1 as a control, being killed at the beginning of the experiment, and the three others after fasting for 7-11 days. Below are some of the data from the analysis of the carcasses.

COMPOSITION OF BODIES OF RABBITS AS AFFECTED BY STARVATION

	No. 1	No. 2	No. 3	No. 4
Loss of Different Parts—Percent				
Flesh		39.7	45.0	43.4
Skeleton		4.1	Gain	3.3
Pelt		23.3	20.3	20.0
Stomach		20.8	34.8	27.7
Intestines		24.7	50.4	48.2
Liver		56.5	54.4	62.5
Lungs		68.1	62.5	53.3
Kidneys		26.3	29.5	26.9
Heart		29.7	23.4	Gain
Spleen		73.9	69.6	71.7
Weight of Parts in Grams				
Flesh, water and fat-free	210.33	147.00	133.39	137.85
Skeleton, water and fat-free	88.79	95.65	101.26	96.30
Fat in flesh	41.32	4.75	4.98	4.50
Fat in skeleton	11.58	0.52	0.53	0.77
Fat in flesh and skeleton	52.90	5.27	5.51	5.37
Analysis of Bones Other Than Leg Bones—Percent of Water- and Fat-free				
Organic substance	38.06	39.73	37.74	39.35
Mineral substance	61.94	60.27	62.26	60.65
CaO	32.35	31.76	32.52	31.77
MgO	0.71	0.69	0.62	0.64
CO_2	2.50	2.70	2.88	2.48
P_2O_5	24.17	24.02	24.67	24.22
Remainder	2.21	1.10	1.57	1.54
Analysis of Teeth—Percent of Water- and Fat-free				
Organic substance	23.42	21.80	21.52	22.09
Mineral substance	76.58	78.20	78.48	77.91
CaO	37.88	38.75	38.92	38.83
MgO	2.49	2.44	2.49	2.37
CO_2	0.77	0.99	1.10	1.45
P_2O_5	33.91	34.21	34.46	34.24
Remainder	1.53	1.81	1.52	1.02

It will be noted that the leg bones were not included in the above analyses. In an effort to harmonize these results, which do not show a loss of phosphorus from the bones, with those which have been discussed, we can only suggest that the bones constitute, relatively, so large a store of the mineral constituents of the body that a considerable change in amounts of urinary constituents would represent but a slight change in the skeleton as a whole, so slight a change, in fact, that its detection by skeleton analysis would be very likely to be missed through the inevitable errors involved in the comparison of a starved animal with another individual serving as a control; further, the fasting time was short; the skeleton yields but slowly to influences which tend to modify its composition.

Hoover and Sollmann (1897) studied phosphorus metabolism during fasting in hypnotic sleep covering a period of 8 days. The analysis of the urine is as follows:

ANALYSIS OF URINE DURING HYPNOTIC FAST—Grams

Date	Quantity C.C.	Urea	Uric acid	P_2O_5	NaCl	Total N	Water taken
July 15	1350	36.21	0.824	3.381	12.330	20.978	....
" 16	570	22.62	0.617	2.303	6.837	12.369	....
" 17	470	22.99	0.450	2.268	3.863	12.370	750
" 18	530	25.24	0.538	2.270	3.964	14.013	750
"19 & 20	1020	58.18	0.866	5.052	5.954	27.988	1150
" 21	410	20.67	0.375	2.434	2.496	10.791	875
" 22	560	28.26	0.572	3.150	2.419	14.504	1250
" 23	820	34.13	0.908	4.442	3.296	21.582	750

The loss in weight during the last 7 days was 5896 gm.; loss of nitrogen, 113.617 gm.; nitrogen estimated as albumin 710 gm., —estimated as muscle 3341 gm.

There was some evidence of an increased proportion of phosphorus to nitrogen during the progress of the fast. The average loss of phosphorus during the last 7 days was 3.131 gm. P_2O_5.

Nemser (1899) studied the effects of starvation on the total and nuclein phosphorus content of the muscles, liver, kidney and intestine of white mice. Eighty mice were used. The data seem to indicate that the percent of loss in weight of parts was greater than the gain in percent of total and nuclein phosphorus, which implies that the total and nuclein phosphorus contributed to the loss during fast.

Sedlmair (1899) studied the losses sustained by the various organs of the cat during starvation, by comparing three cats of the same litter, one well-fed, with two which were starved. One cat, starved for 36 days, and losing in weight 1764 gm. from an initial

weight of 3368 gm., apparently lost in this time only 0.564 gm. CaO, which was computed to represent 3.4 gm. of fresh bone substance, or less than 1 percent of the total weight of the skeleton. Below are figures which distribute the total loss to the various parts sustaining decrease in weight.

LOSSES IN DRY SUBSTANCE OF DIFFERENT TISSUES OF CATS DURING STARVATION—Percents of Total Loss

	Cat B	Cat C
Muscular system	62.23	57.06
Skin	11.33	16.50
Mesentery	8.51	7.56
Bones	5.67	8.17
Liver	5.03	4.41
Intestines	3.00	3.18
Kidneys	0.80	0.73
Pancreas	0.22	0.41
Heart	0.39	0.31
Lungs	0.24	0.30
Spleen	0.25	0.25
Brain	+0.17	+0.10
Spinal marrow	0.05	0.07
Central nervous system	+0.12	+0.03
Urinary bladder, aorta, trachea and eyes	0.16	0.06
Blood	2.29	1.11
	100.00	100.02

The bones were in most cases made richer in water by starvation, while the dry substance decreased, both absolutely and in percent, these effects being most noticeable in the long bones. The principal loss of weight from the bones was fat, though all other constituents of the bones shared in the loss.

Schulz and Mainzer (1901) studied nitrogen and phosphorus metabolism in 3 starving rabbits and 1 starving dog. They observed in each case the usual premortal rise in the urinary excretion of both nitrogen and phosphorus, but no significant change in ratio of nitrogen to phosphorus in the urine just prior to death. Death occurred before the disappearance of fat from the body.

Rubow (1905) found the lecithin content of 9 normal dogs' hearts to vary between 7.05 and 8.80 percent; while of fat the same hearts contained 3.60 to 3.99 percent, in the dry substance. Two dogs which were starved to death, had in the hearts 7.3 and 7.67 percent of lecithin, and the same hearts contained 3.67—3.71 percent of fat, on the dry basis. In normal dog muscle the lecithin varied between 4.44 and 5.27 percent, while the fat content of the same samples was 14.16 and 6.30 percent, respectively, on the dry basis. In the muscle of the starved dogs was found 3.08 and 3.74 percent of lecithin, and 2.58 and 2.74 percent of fat, on the dry basis.

From these figures it would appear that in starvation the dog uses both fat and lecithin from the muscles, but the withdrawal of either fat or lecithin from the heart is doubtful.

Van Hoogenhuyze and Verploegh (1905), in studying creatinin excretion, publish urine analyses of a human subject, covering 15 days of fast, preceded and followed by one day with food. The figures are as follows:

URINE ANALYSIS OF A FASTING MAN—Grams

Date	Total N	Creatinin	P_2O_5	N/P_2O_5	Remarks
June 10	13.99	1.087	2.670	5.2	Food
" 11	8.76	0.904	1.550	5.8	Beginning of starvation period
" 12	8.38	0.577	1.830	4.6	
" 13	10.73	0.581	2.654	4.0	
" 14	9.40	0.634	2.934	3.2	In the morning, 50 c.c. sulphatic water drunk
" 15	7.87	0.603	1.749	4.5	In the morning, 50 c.c. sulphatic water drunk
" 16	7.73	0.590	1.069	7.2	In the morning,100 c.c. sulphatic water drunk
" 17	6.11	0.469	0.713	8.5	From 11 to 1 o'clock, muscular work
" 18	7.70	0.689	1.658	4.6	
" 19	7.35	0.715	1.702	4.3	
" 20	6.80	0.602	1.461	4.6	
" 21	6.14	0.453	1.097	5.6	
" 22	6.97	0.566	1.312	5.3	
" 23	5.62	0.548	1.114	5.0	
" 24	4.08	0.426	0.869	4.7	
" 25	4.38	0.715	0.539	8.0	Food taken at 10 o'clock at night
" 26	7.23	1.028	0.145	49.9	Food

At the beginning of this fast the nitrogen, phosphorus and creatinin decreased from the quantities excreted during the day before, and, as tissue protein was attacked, the ratio of N to P_2O_5 in the urine became less. The muscular work of the 7th day of fasting had the effect temporarily to lessen the excretion of nitrogen, creatinin and phosphorus, especially phosphorus, though the excretion of all these constituents rose on the next day, the creatinin and phosphorus elimination remaining high for three days. At the end of the fast the total nitrogen and creatinin excretions rose markedly, but the phosphorus excretion sank to a lower figure than at any time during the fast, or on the day before the fast, which implies a lessened katabolism of phosphorized proteins, and the replenishment of depleted phosphorus reserves.

Cathcart and Fawsitt (1907) reported on a 14-day fasting experiment, with a 31-year-old man, with a 3-day preliminary and 5-day after-period, in which nearly one-fifth of the phosphorus seemed to have some source other than the soft parts. During this fast the elimination of purin bases and phosphorus decreased on the first day, the organism apparently sparing its nucleoproteins. The minimum purin excretion was on the third day of the fast, after which it increased, reaching the normal on the tenth day. The phosphorus outgo, however, steadily decreased, as also did total nitrogen, and both were less in amount on the last day of the fast than on any other. Thus purins increased as phosphates and total nitrogen decreased. That nucleins participated in the tissue katabolism is, of course, clear. The fate of the nonpurin nitrogen and of the phosphorus from the nucleins, however, is not so certain

but since the outgo of total nitrogen and phosphorus was undergoing a progressive decrease it would be fair to assume that these constituents were retained, or else, if eliminated, that they served to protect equivalent amounts of the same in a higher state of organization or combination.

Wellman (1908) studied mineral metabolism in fasting rabbits. In experiments of 12-15 days duration it was determined that full-grown rabbits, in starving to death, lost 6.5 to 7.7 percent of the fat-free, dry substance in the bones, and about 14 percent of the fresh weight. Of this loss of fresh weight nearly half was fat. The absolute loss of calcium from the bones was determined as 1.8 gm., of phosphorus 0.6 gm., and of dry substance 8.7 gm.

Falta and Whitney (1908) also found in the fasting metabolism of the dog such an increase in the proportions of Ca and P to N in the urine as indicated a probable participation of the bones in the increased katabolism.

Grund (1910) concluded that the ratio P:N in the organs of animals tends strongly to remain constant under different conditions of nourishment as well as in fasting, though some variation in this proportion was noted in the liver of the hen and the dog. According to recent observations (1912a, 1912b, 1913) the relative amount of protein phosphorus in muscle, in relation to total phosphorus and to the protein nitrogen, is not altered by the wasting away due to hunger, but is materially increased by degeneration due to the severing of nerves or to severing from the bone. Atrophy, from division of the nerve, and from severing from the bone, alike, cause a dissolving of phosphorus-free proteins, with a sparing of phosphoproteins.

Wolf and Œsterberg (1911) made a study of nitrogen, sulphur and phosphorus metabolism in the dog as affected by fasting or underfeeding. The feeding of a comparatively small amount of protein was found to reduce the phosphorus excretion to a very low amount. The feeding of starch and fat seemed to have little or no effect on phosphorus excretion. During fasting the ratio of phosphorus to nitrogen in the urine was so high that it seemed probable that some of the phosphorus came from the bones.

Wilson and Hawk (1914) found that during fast the urinary acidity and phosphates varied, in general, together, increasing amounts of acid in the blood or lymph (due to increased fat katabolism in the presence of decreased carbohydrate oxidation) leading to a change of di- to monophosphates, and the excretion of the excess of the latter. Thus increased phosphate excretion and urinary acidity followed an increased formation of acids in the body. Increased neutralization of acids with ammonia led to decreased urinary acidity and phosphates.

Among the other changes produced by starvation, in the phosphorus compounds of animals, may be mentioned the reduction in the lecithin phosphorus of the liver as noted by Heffter (1890, 1891) and the decrease in the phosphocarnic acid in the brain as observed by Panella (1906a).

Summary. Fasting causes an increased outgo of phosphorus. From the evidence that non-purin nitrogen, as well as nuclein compounds and skeleton, all contribute to this outgo we conclude that its production is due to generalized katabolism. The proportionate losses sustained by the various tissues are difficult of determination. The loss from the skeleton, however, is appreciable, though but a very small part of the total phosphorus present. The lecithin phosphorus of the liver and muscles, and the phosphocarnic acid of the brain have been shown to contribute to the phosphorus loss in starvation.

There is evidence that the first deficiencies of phosphorus are met principally by non-purin compounds, that there is a progressive decrease of phosphorus outgo from this source, and also of total phosphorus, until the premortal rise, but increasing contributions from nuclear and skeletal compounds.

There is evidence of a further utilization by the animal of the phosphorus of katabolized nuclein compounds after the elimination of the purin nitrogen.

The feeding of protein during starvation has a much greater effect to reduce phosphorus loss than the feeding of starch and fat.

PHOSPHORUS METABOLISM DURING INCUBATION

As typical of metabolism generally, especial interest attaches to the simplified physiology of the egg. C. Voit (1877a) sought to determine if there is a loss of lime from the egg-shell, and utilization of the same in the growth of the skeleton of the incubating chick. He concluded that there was no such loss of lime from the shell, but his method of demonstration leaves one in doubt as to the fact.

During incubation A. Kossel (1885) found that the phosphoprotein of the hen's egg changes to nucleoprotein, because, while the yolk nuclein of the fresh egg does not yield purin bases, the nuclein of the hatched chick does yield guanin and hypoxanthin.

Maxwell (1893) studied the phosphorus exchanges in the incubating hen's egg but the analytical data indicate that his methods were unsatisfactory.

Mesernitzy (1907) states that the lecithin of the fresh hen's egg, dried, is about 15.35 percent, estimated from the phosphorus of the ether extract. During incubation he found this amount reduced by about a half.

Carpiaux (1908) shows that with the decrease of lecithin in the incubating hen's egg there proceeds an accompanying decrease in the lime of the shell, and an increase of inorganic phosphates. The following data substantiate these conclusions.

ANALYSES OF HENS' EGGS DURING INCUBATION—Grams

Exp. No.	Age in days	Weight	CaO	P_2O_5, inorganic	P_2O_5, organic	P_2O_5, total	Lecithin
1	0	.....	0.040	0.075	0.150	0.225	1.050
2	6-7	62.63	.....	0.128	0.146	0.274	1.022
3	6-7	55.43	0.0377	.....	.....	.....	.....
4	7-8	64.70	0.0360	0.127	0.135	0.262	0.945
5	13-14	54.20	0.0478	.....	.....	.....	.....
6	14-15	54.62	0.0616	0.137	0.108	0.245	0.760
7	18	55.90	0.1357	0.182	0.050	0.232	0.350
8	19	53.10	0.1487	.....	.....	.....	.....
9	21	.....	0.2022	.....	.....	.....	.....

Plimmer and Scott (1909) compared the phosphorus distribution in the body of the chick at the time of hatching with that of the fresh egg, and of the egg at different times during incubation. They draw the following conclusions with regard to the sources of the different phosphorus compounds of the young bird's body:

"There is not much change in the ether-soluble phosphorus until about the 16th or 17th day of incubation, when a very rapid disappearance of the ether-soluble phosphorus bodies commences. At this time it corresponds with a great increase in the amount of inorganic phosphate in the chicken; therefore it is impossible to avoid the conclusion that these glycerophosphoric acid compounds have been converted into inorganic phosphate for the calcification of the bones.... Some of the inorganic phosphate must have come from the vitellin, since all of it disappeared. Probably some of it, however, was converted into nucleic acid, as the latter increased.... There is a gradual absorption of the protein phosphorus bodies of the yolk by the developing chicken before there is a change in the lecithin bodies."

General Conclusion: "That the glycerophosphoric acid gives rise only to inorganic phosphate in the developing chicken and is not transformed into any combination with protein. There is no evidence of a synthetic process occurring in the developing egg as regards the phosphorus compounds unless the probable transformation of the phosphoprotein into nucleoprotein be so considered."

Data from this study are in the following table.

DISTRIBUTION OF PHOSPHORUS IN HEN'S EGGS AT DIFFERENT PERIODS OF INCUBATION

Percents of Total Phosphorus Present in Egg, Chick, and Rest of Egg

Stage of incubation	Total P_2O_5 in acid solution			Inorganic phosphates in acid solution			Ether-soluble			Residual proteins (includes vitellin and nuclein-like bodies)			Vitellin		
	Egg	Chick	Rest of egg	Egg	Chick	Rest of egg	Egg	Chick	Rest of egg	Egg	Chick	Rest of egg	Egg	Chick	Rest of egg
Unincubated	6.2	....	....	Trace	....	....	64.8	....	....	29.0	....	....	27.1	..	....
After 7 days	8.2	....	....	Trace	....	....	64.1	....	....	27.1	....	....	23.6	..	....
" 13 "	10.1	....	....	Present	....	....	66.0	....	....	24.0	....	....	23.0	..	....
" 14 "	....	56.0	13.8	....	13.2	Trace	....	22.5	61.7	....	21.5	24.4	....	0	18.5
" 16 "	10.2	....	....	Present	....	....	62.3	....	..	27.5	....	....	....	..	....
" 17 "	....	55.0	10.4	....	30.5	Trace	....	17.8	68.7	....	27.2	20.8	...	0	15.8
" 19 "	27.2	67.4	14.1	19.1	50.3	Trace	51.0	14.6	60.2	21.8	18.0	25.7	11.1	0	16.2
" 20 "	52.2	....	....	47.7	....	....	36.0	....	....	16.1	....	....	....	..	....
Hatched	....	68.6	....	....	60.0	....	....	19.3	....	....	12.0	....	....	0	....

Hanes (1912a, 1912b) finds, by microchemical studies, that phosphorized fats are abundant in the liver of the incubating chick during the first two weeks; during the third week these compounds diminish, the phosphorus apparently serving for calcification. It is suggested that the pathological calcification of arteriosclerosis results from a splitting *in situ* of phosphorized fats, with subsequent formation of calcium salts. See also Tornani (1909).

Robert and Wasteneys (1913) concluded that serious errors vitiated the results of Massing and of Shackell in their studies on the phosphorus changes in developing sea-urchin eggs. From an investigation of their own they submit the following data:

FORMS OF PHOSPHORUS IN DEVELOPING SEA-URCHIN EGGS
Percent of Total P

Stage of development	Soluble in alcohol		Soluble in water		Insoluble	
	Exp. 1	Exp. 2	Exp. 1	Exp. 2	Exp. 1	Exp. 2
Eggs	39.5	46.5	36.7	29.6	23.8	23.9
Blastulae	36.5	38.8	47.6	40.6	15.9	20.6
Plutei	35.2	35.1	30.8	37.8	34.0	27.1

The conclusions are as follows:

"1. During the development of the eggs of *Strongylocentrotus purpuratus* to blastulae the proportion of P which is present in the form of phospholipines (lecithin, etc.) undergoes appreciable diminution. The further development of the blastulae into plutei is accompanied by a further diminution in the proportion of phospholipines in the larvae.

"2. The development of the eggs of *S. p.* to blastulae is accompanied by a considerable increase in the proportion of P which is soluble in boiling water and insoluble in alcohol, and by a decrease in the proportion of P which is insoluble either in alcohol or in boiling water. The further development of the larvae to plutei is accompanied, on the contrary, by a decrease in the proportion of water-soluble phosphorus and an increase in the proportion of insoluble P."

PHOSPHORUS METABOLISM IN INFANCY

RELATIVE VALUE OF DIFFERENT KINDS OF MILK

Human milk is low in the ash constituents generally, and also low in phosphorus, as compared with all other milks. It is also low in casein as compared with most of them, including cow's milk. It

has, however, a relatively high content of both phosphatid and nucleon, and of Wróblewski's opalisin, and a relatively large part of its phosphorus is in an organic form. Each of these items has been brought forward as an explanation of the undoubted fact that children thrive better, and form bones and tissues more rapidly, when they are fed on mother's milk than when artificially fed.

In composition, the milk of equidae is most nearly like human milk. Schlossmann (1897) considered ass's milk with a view to its value as a substitute for human milk, but decided that it would be unsatisfactory on account of its high proportion of protein to fat.

Aside from differences in amounts, the caseins are found to be different in kind, the evidences being reported in our discussion of the chemistry of casein on pages 43 and 44.

Soxhlet (1893) discusses differences between human and cow's milk, with consideration of suitable modifications of cow's milk to prepare it for the human infant. He says that cow's milk gives coarser clots with rennet ferment, and contains about twice as much casein and 6 times as much calcium, and has 3 times as high acidity, as human milk. Addition of water, or heating the cow's milk, reduces the size of colts; but in each case other effects produced are unfavorable. Decoctions of grains, etc., affect the clots as do corresponding amounts of water, but add starch; if malt extract be added the resultant mixture may be of higher nutritive value. Since cow's milk contains 4 times as much phosphoric acid and 6 times as much calcium as human milk, more calcium phosphate is supplied than is needed for bone-formation, and the excess is excreted, mostly as calcium soaps in the feces. Both kinds of milk contain the essential soluble calcium, principally in the form of calcium citrate.

Julius Lehmann (as reported by Hempel, 1894) and Hammarsten (1895) both proposed modification of cow's milk for the use of human infants, on the basis of the consideration that the most significant difference between human and cow's milk is in the ratio of albumin to casein, and of casein to fat.

Stoklasa (1897) gives the range of lecithin in cow's milk as 0.90-1.13 gm. per liter (representing an average of 0.091 gm. P_2O_5), and that in human milk as 1.70-1.86 gm. per liter (representing an average of 0.153 gm. P_2O_5). In cow's milk the total P_2O_5 is 1.81 gm. per liter, and therefore the lecithin phosphorus forms 5 percent of the total; while in human milk there is but 0.44 gm. P_2O_5 per liter, and the lecithin, therefore, forms a much larger proportion, 35 percent, of the total.

Blauberg (1897c), studying the nutrition of infants on woman's milk and on cow's milk diet, found about the same differences in the mineral constituents of the feces as in ash of the two kinds of milk, especially a larger calcium and phosphorus, and lower iron content in the feces from cow's milk.

Blauberg (1897b) reports an analysis of Mellin's Food. For comparison with these figures we have computed to the dry basis the proximate food constituents of human milk as reported by Ellenberger, Seeliger and Klimmer (1902), and the mineral constituents as reported by Söldner (1902). From these data it would appear that the use of Mellin's Food with milk would tend to substitute carbohydrates for fats, and to decrease the calcium. The phosphorus content, on the dry basis, is not less than in human milk, and as Mellin's Food is used not with human but with cow's milk, which contains much more calcium and phosphorus than does human milk, it seems likely that the use of this proprietary food would not have the effect to starve the infant for any of the mineral nutrients.

COMPARISON OF THE DRY MATTER OF MELLIN'S FOOD AND HUMAN MILK

	Water, percent	Percents of dry substance									
		Protein	Fat	Carbohydrate	Mineral matter	K_2O	Na_2O	CaO	MgO	P_2O_5	Cl
Mellin's food	6.31	8.2	2.22	85.15	3.93	1.15	0.41	0.025	0.047	0.38	0.081
Human milk	86.4	11.8	35.3	48.5	1.84	0.65	0.26	0.28	0.039	0.23	0.43

For other analyses of infant foods see Blauberg (1897a), Klautsch (1896), and vonSzontagh (1902).

Keller (1898) determined that when feeding infants on cow's milk more phosphorus is found in the urine than under normal feeding, and also a very much larger proportion of phosphorus to nitrogen.

Keller (1900b) studied nitrogen and phosphorus metabolism with infants, both normal and suffering from gastrointestinal disorders, on normal and on artificial milk feeding. By the addition of $Na_2H\ PO_4$ to human milk the phosphorus retention was increased in either well or sick infants. Phosphorus retention was greater on human milk than on cow's milk.

Balance data from Keller's studies are in the following table.

AVERAGE DAILY NITROGEN AND PHOSPHORUS METABOLISM OF HEALTHY AND DISEASED CHILDREN ON NATURAL AND ARTIFICIAL MILK DIETS—Grams

Exp. No.	Child No.	Length of exp. Days	Age of child Mos.	Initial weight	Gain in weight	Nitrogen				Phosphorus (P_2O_5)				Diet
						Food	Feces	Urine	Percent retained	Food	Feces	Urine	Percent retained	
I	1	4	3¼	3690	+12.5	1.438	0.124	1.116	15.1	0.519	0.107	0.335	18.8	One-third cow's milk plus Na_2HPO_4
II	2	5	5	4190	+22.0	1.512	0.290	0.755	38.2	0.280	0.091	0.090	52.3	Woman's milk plus Na_2HPO_4
III	2	5	5½	3960	−12.5	2.050	0.275	1.606	9.5	0.857	0.333	0.364	23.1	One-half cow's milk plus Na_2HPO_4
IV	3	5	2¼	4380	+10.0	1.408	0.209	0.770	35.8	0.240	0.050	0.062	67.5	Woman's milk
V	4	5	2¼	3190	−22.0	1.132	0.171	0.694	27.9	0.188	0.050	0.105	23.6	Woman's milk plus Na_2HPO_4
VI	4	5	2½	3300	+28	1.601	0.304	0.623	51.9	0.268	0.082	0.088	53.0	Woman's milk plus Na_2HPO_4
VII	4	5	2¾	3530	+44	1.730	0.223	0.568	62.3	0.820	0.161	0.386	41.3	Woman's milk plus Na_2HPO_4
VIII	5	5	2	4350	+28	1.875	0.244	0.788	51.7	0.325	0.051	0.098	64.0	Woman's milk
IX	6	5	10	4380	+48	4.775	0.296	3.599	19.7	0.970	0.899	0.851	20.5	Cow's milk, whole, plus Na_2HPO_4
X	1	5	5	3640	+6	1.875	0.409	0.863	41.2	0.850	0.347	0.424	15.9	Malted milk plus Na_2HPO_4
XI	4	5	4	3630	+14	1.528	0.433	0.608	44.5	0.264	0.062	0.116	42.3	Woman's milk plus Na_2HPO_4
XII	5	5	2¾	4900	−6	2.226	0.141	1.326	36.4	0.825	0.107	0.411	42.7	Two-fifths cow's milk
XIII	4	5	4¼	3550	−4	1.357	0.188	0.938	19.8	0.481	0.080	0.363	8.7	One-third cow's milk plus Na_2HPO_4

Children Nos. 1, 2, 4 and 6 were pathological cases; Nos. 3 and 5 were healthy.

Netter (1900) found the density of the urine, and its content of nitrogen, phosphorus and calcium higher with artificially fed than with normally fed infants. The amount of feces was greater with the infants on cow's milk, and their content of calcium and phosphorus was also higher. Netter reported balance data from 7 infants on sterilized cow's milk as the exclusive diet. A part of the figures follow.

AVERAGE DAILY BALANCES OF NITROGEN, CALCIUM AND PHOSPHORUS PER KILOGRAM BODY WEIGHT WITH HEALTHY INFANTS ON STERILIZED COW'S MILK

Grams

No. of subject	Weight	Duration in days	Milk consumed C.C.	N Balance	CaO Food / Urine / Feces / Balance	P_2O_5 Food / Urine / Feces / Balance	Age Months
1	7270	4	168	+0.199	0.297 / 0.004 / 0.198 / +0.095	0.344 / 0.071 / 0.182 / +0.09	8
2	5860	3	137	+0.303	0.211 / 0.006 / 0.177 / +0.027	0.342 / 0.095 / 0.197 / +0.049	10.5
3	7310	4	122	+0.133	0.189 / 0.004 / 0.16 / +0.024	0.307 / 0.096 / 0.184 / +0.025	10.5
4	4710	4	170	+0.305	0.263 / 0.007 / 0.229 / +0.026	0.427 / 0.057 / 0.3 / +0.068	7.5
6	8300	3	121	+0.118	0.236 / 0.009 / 0.125 / +0.101	0.298 / 0.06 / 0.184 / +0.052	9.0
7	6980	3	148	+0.165	0.248 / 0.010 / 0.16 / +0.077	0.294 / 0.096 / 0.122 / +0.075	7.5

Netter gives as the average gains of these infants the following:

	Average gain per day	Average gain per kilo per day
Body weight	11.64	1.772
Nitrogen	1.26	0.194
CaO	0.395	0.058
P_2O_5	0.402	0.059

Comparing these figures with results of Michel, Netter finds that the gain in nitrogen, calcium and phosphorus is about the same as for new-born naturally-fed infants, although less regular. The gain in weight is said to be less. The author appends 118 references.

P. Müller (1900) investigated the nucleins and lecithins of the feces of infants, adults, calves and dogs, and found that cow's milk casein in the intestine of the normal infant leaves no more digestion-residue rich in phosphorus than does the casein of woman's milk; also that adults utilize the casein phosphorus of cow's milk as completely as do infants. Lecithin was found in milk feces and was considered as derived from the food.

Von Szontagh (1902) conducted two 4-day balance experiments on an infant with "Székely's milk," a modified cow's milk, from which the casein had been precipitated by liquid carbon dioxide. The nitrogen was apparently absorbed to the extent of 90.37-92.20 percent of the intake, the phosphorus 65.26-60.05 percent, and the calcium 10.79-15.33 percent. The retention was 0.679-0.810 gm. nitrogen, 0.218-0.542 gm. P_2O_5 and 0.086-0.105 gm. CaO.

Cronheim and Muller (1903) studied the effects of sterilization of milk on its utilization by infants. The results on phosphorus retention were inconclusive. Later studies on the same subject showed that sterilization of milk is probably without influence on phosphorus metabolism.

Tangl (1904) conducted two four-day balance experiments with infants on "Székely's milk." The composition of the milk was said to be as follows: Water 87.2; fat 3.7; casein 1.5; albumin 0.9; milk sugar 6.3 and ash 0.7 percent.

The milk as analyzed for the two experiments was composed as follows:

Analyses of Székely's Milk

	I	II
Solids	13.13	13.11
Organic matter	12.58	12.57
Ash	0.555	0.534
Total N	0.293	0.344
Protein N	0.261	0.331
Casein N	0.235	0.307
Albumin N	0.026	0.024
Non-protein N	0.033	0.013
Sugar	6.53	6.32
Calories in 100 gm.	67.31	71.32
K	0.163	0.163
Na	0.031	0.032
Ca	0.083	0.084
Mg	0.0095	0.0097
Cl	0.103	0.084
S	0.013	0.017
P	0.069	0.074

The apparent absorption of N was 90.0-92.3 percent of the intake. The retention of nitrogen was 23.4-29.9 percent, of Ca 11.5-14.2 percent, and of P 18.6-38.5 percent of the intake.

Schlossmann (1905a, 1905b) says that during the first year of an infant's life it retains 55-60 gm. P. He shows that the phosphorus content of artificial milk mixtures is not likely to fall below the normal for human milk. He submits data showing that infants absorb much more phosphorus from mixtures of cow's milk and cream, or buttermilk and cream, or from buttermilk alone, than from woman's milk.

Bruck (1908), in metabolism experiments on artificially nourished infants, found about three times as much phosphorus in the urine as in the feces, which implies satisfactory absorption. The numerical data are as follows.

PATHS OF EXCRETION OF PHOSPHORUS AND THE MINERAL BASES WITH INFANTS—Grams

Exp. No.	Constituents	Intake	Urine	Feces	Percent of retention
I 4 days	CaO	2.4098	0 1944	1 0229	45.3
	MgO	0.6392	0 0269	0 1815	67.2
	P_2O_5	2.8795	1.7086	0 5001	23.5
	K_2O	2.7775	1.2374	0 4243	40.2
	Na_2O	1.7190	0.7942	0.0547	50.6
II 3 days	CaO	2.2276	0 1094	1.2190	40.3
	MgO	0.3105	0.0520	0.0739	59.5
	P_2O_5	4 3624	2.5091	0.9521	26.3
	K_2O	3.9396	4.2613	0.1733	
	Na_2O	2.6684	1.9060	0.0143	28.0

The diet was milk, gruel and malt.

Friedenthal (1911) reviewed the knowledge on the ash constituents of different varieties of milk in connection with the artificial feeding of infants. A table gives the anions and cations per liter of the milk from woman, cow, sow, dog, rabbit and ass.

These comparisons of the milk of the various species of animals, as food for infants, lose somewhat in practical significance, as also do the observations on proprietary infant foods, and the old-fashioned modification of milk with water, since the modern method of "split-protein" feeding, which is based on the modification of milk with whey, has come into prominence. Through the use of skim milk, whey, cream and milk sugar; all from cow's milk, an artificial food is prepared which may be varied in the details of its composition in such ways as exactly to suit the requirements of any

particular infant. This system has made possible a new era in successful and scientific infant feeding. The use of evaporated whey in powder form lessens the labor incident to the preparation of the milk by this process. The advantages of this system are (1) that it allows of the control of the proportions of fat and protein, (2) that it makes possible the increase of the normal proportion of albumin to casein, an advantage to delicate infants, and (3) that it assists in the prevention of rachitis and other disturbances of mineral metabolism in infants, by providing, through the use of whey, against the possibility of a deficient intake of calcium, phosphorus and other mineral nutrients due to the dilution of cow's milk with water according to the old method, and also against excessive outgo of calcium in soap stools.

Some additional references on the consideration of suitable milk for infant feeding are listed below: Langgaard, 1875; Biedert, 1874, 1880, 1884, 1887, 1897; Schmidt, 1882; A. V. Meigs, 1883; Schlossmann, 1896; Wróblewski, 1894a, 1894b, 1898; Siegfried, 1897; Edlefsen, 1901; W. Camerer, Jun. and Söldner, 1903.

MISCELLANEOUS DATA ON PHOSPHORUS METABOLISM OF INFANTS

Michel (1897) shows that of all the constituents of the mother's milk the minerals are, in general, least well utilized, as indicated by comparison of food and feces. The phosphorus was utilized in a case under observation to the extent of 91.63 percent, the food phosphorus being 0.263 gm. (P_2O_5) in 566 gm. milk, and the feces phosphorus 0.022 gm. in 2.99 gm. dried feces.

Oechsner (1899) determined the nitrogen and phosphorus in the urine of nursing infants. The 24-hour quantity varied from 0.04 to 0.12 gm. P_2O_5, and the proportion of $N:P_2O_5$ from 5.2:1 to 10.4:1.

Keller (1900a) determined that the organic phosphorus of the urine of infants was greater in amount after feeding cow's milk than after feeding human milk, though it was a smaller percentage of the total urinary phosphorus, since the total phosphorus from the cow's milk greatly exceeded that resulting from woman's milk. It varied in amount from less than one to about 10 percent of the total urinary phosphorus.

Camerer, Söldner and Herzog (1902) came to the conclusion that of the ash constituents given in the first month of the life of the human infant (about 1.4 gm. daily) about 50 percent is used for the growth of the body, and that among these relatively the largest amounts are retained of lime, magnesia and phosphoric acid; apparently more than 65 percent of the amounts given.

W. Freund (1905) studied the influence on metabolism of variation in the fat content of the milk of infants. Increasing the fat increased the urinary ammonia coëfficient, decreased the feces phosphorus, and increased the phosphorus retention. The increased phosphorus retention was explained as due to improved absorption, a part of the calcium ordinarily excreted combined with phosphorus in the feces being excreted in this case combined with fatty acids, thus leaving a corresponding amount of phosphoric acid free to be absorbed.

Michel and Perret (1906) report figures for the metabolism of calcium and phosphorus by four infants four-and-a-half to five-and-a-half months of age showing that calcium is utilized to the extent of 13.05-60.22 percent. A part of the variation in the apparent utilization, as above stated, is due to variability in the excretory function of the intestine, the percent of utilization being determined by a comparison of food and feces only, while comparatively trivial circumstances may deflect katabolized nutrients from urine to feces.

Heubner (1909) submits the following data showing the extent of the urinary excretion of phosphorus by infants.

PHOSPHORUS EXCRETION IN THE URINE OF HEALTHY INFANTS

Age	Food	Weight Kg.	Phosphorus per day per kg. body weight Grams	Phosphorus, in percent of urine	No. of analyses
New-born.....	.....	3.16	0.0003	0.0018	2
6 weeks.....	Mother's milk	4.85	.....	0.0012	
3-5 weeks.....	" "	3.86—4.38	0.0017	0.0022	4
8-16 weeks.....	" "	4.05—6.80	0.0010	0.0012	5
5 weeks.....	" "	5.23	0.0007	0.0039	
2-6 weeks.....	" "	3.98—4.80	0.0027	0.0025	4

Moll (1909) concluded that there is no phosphorus, or at the most very small amounts, in the urine of the normal breast-fed infant, but that indigestion causes some elimination of phosphorus by this channel. Organic phosphorus in the urine of a breast-fed infant is regarded as a pathological symptom.

Heubner (1910) determined the phosphorus (P) of the urine of the new-born infant as 0.0018 percent, and the phosphorus of the amniotic fluid as 0.003 percent. These values are about the same as those reported by other investigators from blood serum, from which Heubner suggests that we may consider 0.002 percent P as the physiological concentration of body fluids in soluble phosphates, which filter out into the urine, and that this is the minimum value for urine content from this source. See also Langstein and Memann (1910).

Koeppe (1911) studied urinary phosphorus elimination in infants as affected by amount and kind of food, and by NaCl added to the food. The urinary phosphorus was found to vary with the amount of food, if the kind remained the same, and with the kind, if the quantity remained the same. There is some evidence tending to show increased concentration of phosphorus in the urine following the ingestion of sodium chloride, but the results are hardly sufficient to establish the fact. The ingestion of NaCl brought about an increase of temperature and a chlorine retention.

When infants are given more casein in the milk than they are able to digest, especially as in feeding on unmodified cow's milk, there may occur in the feces hard, white, or yellowish lumps of undigested curd, having much the same appearance as the lumps of soap in the feces sometimes resulting from an excess of fat in the milk (Monrad, 1911; Uffenheimer and Takeno, 1911; J. Bauer, 1911; Ibrahim, 1911; and Brennemann, 1911). The soap and curd lumps are commonly distinguished by their behavior under the influence of heat.

Tobler (1911) published studies of alterations in the composition of the muscles of infants after death from disorders involving acute or chronic loss in weight. The ash content of the muscles of atrophic children was very low, but the phosphorus content of the ash was not subnormal. The ash of the fat-free, dry muscle varied between 3.164 and 4.724 percent, while the phosphorus in the ash varied between 7.16 and 14.63 percent. Primary water-loss was considered to have led to salt-loss. See also Birk (1911).

E. Müller (1911) thought that the ill effects of feeding infants on undiluted cow's milk are due to excess of whey constituents other than sugar, and submitted balance data in support of his idea. This is not the prevailing view.

Hoobler (1911) shows that increasing the fat of the food of infants increases the percentage of the phosphorus of the food which is absorbed. With milk containing 2.1 percent fat, 67 percent of the phosphorus was absorbed; with 4 percent milk the phosphorus absorption was 78.1 percent, while with 5.4 percent milk, 83 percent of the phosphorus was absorbed.

Schloss and Crawford (1911), studying phosphorus metabolism in the new-born infant, found a marked diminution in the phosphorus excretion after the first three days, there being an inverse relation between the leucocyte count and the elimination of phosphorus and uric acid during this period, both apparently having an origin in cell nuclei.

For determinations of the phosphorus and other mineral elements of the food of infants and children see Hoobler (1912).

G. Wolff (1912a) conducted metabolism experiments with infants involving quantitative variation in the diet. He concludes that the change from scanty to abundant diet produces no unfavorable effect on the metabolism of nitrogen, phosphorus and calcium, and that calcium and phosphorus are likely to be deficient in diets which contain nitrogen sufficient only for maintenance or slight storage.

McCrudden and Fales (1912), studying intestinal infantilism, found, in two cases, poor absorption of nitrogen, sulphur, phosphorus, calcium and magnesium. Calcium was excreted in the feces in amounts greater than the intake; the other elements were in part retained.

Jundell (1913) found normal calcium and phosphorus absorption and retention (unlike the other minerals) with 2 children suffering from dyspepsia, and 2 with intestinal intoxication. This result is ascribed to the effects, on the solubility of the tertiary and secondary phosphates, of the abnormal amounts of fermentation acids present.

Giffhorn (1913) studied the effects of variations in the fat and in the whey constituents of the diet of infants as affecting mineral metabolism. With healthy children the fat in the diet favored nitrogen, phosphorus and magnesium retention, while with reference to calcium the results were inconclusive. There was not noted an increased mineral retention resulting from the whey-rich diet as compared with one containing less of the whey constituents.

Takeno (1913) studied intestinal elimination by children in 18 experiments under varied dietary conditions. The close relationship of calcium and phosphorus was apparent. Phosphorus elimination was lowest on nurse's milk diet, and comparatively low also on milk modified with whey; it was highest on a mixed diet. Digestive disturbance diminished fecal phosphorus elimination. The effects of cream and of lipanin on phosphorus elimination in the feces was doubtful or lacking, while cod-liver oil produced a marked effect on both calcium and phosphorus.

Kaminer and Mayerhofer (1913) concluded, from a study of the urine of 50 artificially fed infants, that the metabolism of children so nourished is not normal, that there is regularly a slight phosphaturia, and that this phosphaturia increases with intestinal indigestion or increasing concentration or carbohydrate content of the diet. The organism may then adjust itself to the dietary change, and the urinary phosphorus elimination will fall again.

For phosphorus requirements of infants see p. 414.

Dröge (1913) studied the effects of extirpation of the blood glands, the testicles, the thyroid and especially the spleen from suckling dogs, having in mind Czerny's idea of congenital insufficiency in these organs as a cause of exudative diathesis in human infants. A part of the numerical results are to be found in the discussion of the thyroid glands in relation to phosphorus metabolism. A certain amount of modification of the metabolism of the dogs was produced by the removal of these glands, as made evident by various details of composition, including calcium and phosphorus content.

Summary. In accord with the relatively slow growth of the human infant the ash and the phosphorus contents of woman's milk are low in comparison with the milk of the lower animals. It has, however, a higher content of phosphatid and nucleon phosphorus, a relatively large proportion of the total phosphorus thus being in an organic form, and the phosphorus retention from woman's milk is greater, in proportion to the intake, than from cow's milk.

Because of the higher fat and casein content of cow's milk than of woman's milk, the former, when fed to infants, requires much dilution, which reduces the calcium and phosphorus more nearly to the amounts present in woman's milk and reduces the lecithin and nucleon phosphorus to amounts very much lower than those found in woman's milk. This fact has been considered to warrant the early introduction of egg-yolk into the diet of the artificially fed infant.

From undiluted cow's milk infants may absorb and retain much more phosphorus than from woman's milk, but the ability of infants to do so varies much with the individual.

The phosphorus of cow's milk appears to be more efficiently absorbed than the calcium of the same; more total and organic phosphorus is found in the urine of infants fed on cow's milk than in the urine of infants receiving the mother's milk; also a much larger proportion of phosphorus to nitrogen is found in the urine from cow's milk feeding.

Sterilization of milk seems to be without any such effects on phosphorus metabolism as are ascertainable in short balance experiments.

The modification of milk with whey, instead of water, is in many ways advantageous, and provides against the possibility of deficiency of minerals. The feeding of excessive quantities of whey solids, made possible by the use of evaporated whey, has been known to produce oedematous manifestations in delicate infants, apparently through the superabundance of mineral salts provided.

There is, at the most, but very little phosphorus in the urine of normal breast-fed infants, but urinary phosphorus is considerable on a mixed diet, and is increased by indigestion. Organic phosphorus in the urine of breast-fed infants is regarded as a pathological symptom.

There is a diminution in the urinary phosphorus and uric acid excretion of new-born infants, after the first few days, and a coincident inverse variation in the leucocyte count.

With artificially fed infants there is a slight phosphaturia which increases with intestinal indigestion or with carbohydrates in the diet.

Increasing the fat of the food increases the urinary ammonia and favors phosphorus absorption and retention.

Absorption of the minerals is deficient in infantilism, but in intestinal indigestion and in dyspepsia the calcium and phosphorus absorption and retention may be normal.

For further information on this matter see Phosphorus Requirements of Infants, pages 414-419.

EFFECTS OF MENTAL WORK ON PHOSPHORUS EXCRETION

In view of the vividness of ones consciousness of his own mental operations it becomes a matter of interest to consider the extent of the metabolic accompaniments. One does not readily accept, without question, the dictum that intense mental effort produces no recognizable end products.

Byasson (1868) studied urine composition as affected by mental work, rest and exercise, the diet being controlled by analysis. The P_2O_5 of the urine during rest was 1.508 gm. per day, during muscular activity 1.4779 gm. and during cerebral activity 1.9777 gm. These differences in outgo are not characteristic of the results of later work. See also Wood, L. H., (1869).

Speck (1882) failed to determine an increase of oxidation, as a result of mental work, by examination of the inspired and expired air.

Mairet (1884b) studied metabolism as affected by mental work. A part of his data are the following:

TWENTY-FOUR HOUR URINE DATA AS AFFECTED BY MENTAL WORK

Grams

Condition	Mixed diet		Vegetable diet		Low diet	
	Nitrogen	Alkali phosphoric acid	Nitrogen	Alkali phosphoric acid	Nitrogen	Alkali phosphoric acid
State of rest	24.54	1.65	10.82	1.16	12.13	1.13
After mental work	22.00	1.53	8.45	1.10	10.71	0.99

We see here no evidence of increased metabolism as a result of mental work.

Schtscherbak (1890) studied phosphorus metabolism as affected by mental work. The results do not warrant conclusions. The author states that he found the venous blood from the brain to contain 0.07-0.12 parts per 1000 less P_2O_5 than the arterial.

Preysz (1891, 1892-3) found no increase of urinary phosphorus after mental exercise.

Mainzer (1902) reviewed the literature of the subject of metabolism as affected by mental activity, and at a later date (1903) reported on studies of metabolism during fast, and as affected by mental work, and protracted wakefulness. Urinary analyses only were made. Mainzer considered the curves of elimination of nitrogen and phosphorus, as affected by mental work and by protracted wakefulness, to be similar, both being fatigue curves.

Gilbert and Posternak (1903) determined in metabolism experiments that neither prolonged brain activity nor extreme nervous excitement produces any certain effect on urinary phosphorus elimination. Such variations as were noted seem to be within the normal range.

Aron and Hocson (1911a) studied nitrogen and phosphorus excretion in the urine as affected by mental work. The results as submitted are inconclusive.

DAILY NITROGEN AND PHOSPHORUS EXCRETION IN THE URINE DURING PERIODS OF REST AND MENTAL WORK—Grams

Condition	Subject	N	P_2O_5
Rest, 2 days	Prisoner D	11.01	1.42
Mental work, 2 days	" "	12.96	1.85
Rest, 2 days	" "	11.41	1.56
Rest, 2 days	" H	13.75	2.14
Mental work, 2 days	" "	13.77	2.42
Rest, 3 days, 1st day	" E	9.09	1.65
Rest, 3 days, 2nd day	" "	8.80	1.13
Rest, 3 days, 3rd day	" "	9.01	0.91
Mental work, 3 days, 1st day	" "	8.66	1.08
Mental work, 3 days, 2nd day	" "	8.41	0.98
Mental work, 3 days, 3rd day	" "	9.13	1.28
Rest, 2 days, 1st day	" "	8 45	1.29
Rest, 2 days, 2nd day	" "	8.76	1.25

Voit (Hermann's Handbuch) determined long ago that the total phosphorus content of the nervous system of an adult human being is about 12 gm. P_2O_5, of the muscles about 130 gm. and of the bones about 1400 gm. With these figures in mind, and considering the normal variability of the phosphorus outgo under apparently constant conditions, and the fact that the brain is not a highly vascular organ, one would not be led to anticipate marked or even

appreciable effects of brain work on total phosphorus outgo. At the same time, however, we must note that these experimental data do not prove that there is no increased katabolism of the brain tissue during mental work. They simply do not prove that there is such increase.

PHOSPHORUS METABOLISM AS AFFECTED BY NERVE STIMULATION

Weyl and Zeitler (1882) studied the composition of rabbit's muscle as affected by electrical stimulation, with especial reference to the acid reaction developed. They state the supposition that the process is a union of phosphoric acid, resulting from katabolic decomposition, with K_2HPO_4 to form $2KH_2PO_4$. In an effort to learn the source of the free phosphoric acid involved in the reaction Weyl and Zeitler estimated the total and lecithin phosphorus in resting muscles and in others stimulated for 30-50 minutes. Fresh muscle they found to contain (7 determinations) 0.65-0.82 percent of lecithin, and stimulated muscle (3 determinations) 0.62-0.665 percent. Inorganic phosphates, however, increased consistently and to a marked extent. A part of the data are as follows:

PHOSPHATE AND LECITHIN CONTENT OF RABBIT MUSCLE AS AFFECTED BY STIMULATION

Experiment	State of muscle	Length of stimulation Minutes	Weight of muscle in grams	Inorganic phosphates Percent	Lecithin Percent
I	Resting	30	72	0.308	0.669
	Stimulated		75	0.357	0.665
II	Resting	45	54	0.262	0.707
	Stimulated		53	0.318	0.623
III	Resting	50	71	0.341	0.816
	Stimulated		65	0.362	.....
IV	Resting	45	79	0.288	0.709
	Stimulated		71	0.334	0.655

Since the lecithin phosphorus decrease does not account for the inorganic phosphate increase the authors conclude that this increase of phosphates takes place at the expense of the nucleins—which were not estimated.

Krchivetz (1900) investigated phosphorus elimination as affected by nerve stimulation in rabbits, but the results seem to us to be of doubtful significance. The same may be said of the experiments of Malerba (1905), who studied the phosphorus compounds in both venous and arterial blood from the brain of the dog, before and after subjection to pain. No important differences were observed.

The function of inorganic phosphate in the physiology of striated muscle is explained by E. B. Meigs (1912) in brief as follows: Stimulation of muscle causes the production of lactic acid, the presence of which in the muscle fibers causes the sarcostyles to swell at the expense of surrounding sarcoplasmic spaces, the shortening of the muscle resulting from the increased volume of its sarcostyles. The relaxation of the muscle is brought about by the combination of the lactic acid with the potassium phosphate contained in the muscle fibers.

See also the work of Siegfried and of Cavazzani on phosphocarnic acid metabolism p. 303-305.

EFFECTS OF EXERCISE ON PHOSPHORUS METABOLISM

Pettenkofer and Voit (1866) reported results of complete food studies on man by metabolism and respiration experiments. In connection with this work urinary phosphorus estimations were made which showed that with a medium diet urinary phosphorus was not increased by work.

Flint (1871) studied metabolism as affected by protracted walking. The urinary excretion of phosphorus was much greater during the period of walking than in fore- and after-periods of moderate exercise. During the walking days the phosphorus outgo varied almost as the distance covered.

Walking day	Miles walked	P_2O_5 of urine Grams
3	92	6.625
1	80	5.504
4	57	4.296
2	48	4.674
5	40.5	3.725

Engelmann (1871) in studying the effects of exercise on metabolism concluded that no parallelism exists in the excretion of urea, phosphoric acid and sulphuric acid. The food and water ingested were controlled, and amounts kept constant. The exercise consisted of walking, running, hill climbing, digging, chopping and sawing, and was carried to the point of fatigue. Great thirst was experienced during periods of activity. The experiments, three in number, were 6-8 days in length, half of each experiment being spent at exercise and half at rest. There were, in two cases out of three, slight increases in the urinary excretion of phosphorus and sulphur during work. In the third case the urine and feces phosphorus together, in the work period, slightly exceeded the same during rest, though urine phosphorus alone was slightly lower during work.

Penzoldt and Fleischer (1882) studied urinary phosphorus excretion in dogs as affected by dyspnoea, etc. Dyspnoea, with the attendant increased muscular work, caused increased phosphorus outgo, followed afterward by such decrease as left average figures without great change. The lack of oxygen alone caused an increased phosphorus outgo which persisted into the after-period; while apnoea caused a decreased phosphorus outgo followed afterward by a strong increase. See also Speck (1882).

Pavy (1876a, 1876b, 1877) made studies of the urine of E. P. Weston, as affected by protracted walking. While there was apparently a great increase in phosphorus elimination as a result of the exercise, there were no phosphorus determinations on either food or feces.

North (1883-4) concluded, as a result of experiments on himself, that phosphorus elimination is not increased by work, unless the labor be severe. In three experiments the results showed, on the whole, no important effects on nitrogen or phosphorus outgo.

Mairet (1884a) studied urinary phosphorus elimination as affected by exercise and mental work. With exercise, on a meat diet, the urinary phosphorus was not changed; on a mixed diet, it was increased from 2.11 to 2.27 gm., and on a vegetable diet from 2.03 to 2.37 gm. In the second case the alkali phosphates increased from 1.57 to 1.74 gm., and in the third from 1.52 to 1.92 gm. Urinary nitrogen was also increased by exercise.

Preysz (1891, 1892-3) determined his own daily urinary phosphorus excretion during 10 days. The maximum excretión was 3.00 gm., minimum 2.56, mean 2.784 gm. P_2O_5. During the eleventh day exercise was taken, and the phosphorus excretion rose to 4.17 gm. A return to the method of life of the first 10 days reduced the urinary phosphorus outgo to 2.616 (mean). Further tests gave concordant results.

Klug and Olsavszky (1893) studied urinary phosphorus elimination with a dog as affected by exercise and by lactic acid intake. The average outgo for a 10-days preliminary period of inactivity was 0.3175 gm., the largest amount being 0.39 gm., and the smallest 0.24 gm. During one day of activity the excretion was 0.57 gm., and in the next day of inactivity 0.28 gm. This increase of phosphorus excretion in activity the authors believe to be due to the solvent effect of the lactic acid formed. In a direct test of the effect of lactic acid ingestion on phosphorus elimination the results are inconclusive, though they would be decisive in showing increased urinary phosphorus with lactic acid ingestion were it not for the data representing the fore-period.

I. Munk (1895) studied the effect of exercise, on a constant diet, on the urinary excretion of nitrogen, sulphur, phosphorus, calcium and potassium. Calcium was also determined in the feces. An increased excretion of phosphorus as a result of exercise was clearly shown. The evidence as to increased calcium excretion is less satisfactory. Munk considers that the data show a certain amount of decomposition of bone tissue as a result of work.

Dunlop, Paton and Stockman (1897-8) investigated the subject of the influence of exercise, sweating and massage on metabolism generally. In connection with this study observations were made on phosphorus excretion. These authors show that excessive muscular work causes an increased phosphorus outgo, apparently from the katabolism of muscle substance, and that with individuals out of condition there may be a more deep-seated waste of tissue, involving the nucleins, as indicated by increased excretion of uric acid. Sweating and massage were found without influence on phosphorus excretion. Thus exercise causes katabolic changes in the nitrogenous tissues of persons out of condition that are not produced in the bodies of men in training.

Garratt (1898) investigated metabolism as affected by exercise and Turkish baths. The exercise consisted of bicycle rides, 3 of 80 miles, one of 71, one of 47 and one of 41 miles. The subject was in good physical condition, and the fatigue induced was never excessive. The diet was of normal mixed character, but was not analyzed.

This exercise caused an excretion of urea rising to a maximum of possibly double the normal in about 12 hours, and only regaining the usual level after 30 hours or more had elapsed, this increase beginning immediately after, but not during the exercise.

Uric acid excretion was also increased, possibly during and certainly immediately after the exercise, the height of the rise, and duration of the increase being less with a subject in good condition, and with sufficient food, than with a subject out of condition, or on insufficient food. Phosphorus elimination was increased, not during the exercise but immediately after.

Sulphate excretion was also increased, the rise commencing during the exercise, and reaching a maximum of perhaps 3 times the normal within six hours.

The Turkish baths were without notable effect on phosphate, uric acid, urea or sulphate excretion, but caused a reduction in the excretion of chlorides.

The data submitted include tables showing the effects of ordinary meals, and of an isolated meal, on urinary elimination. The variations due to meals seem quite considerable in comparison with those noted as results of exercise. Accurate control of the food consumed during the exercise experiments would have been desirable.

In connection with the above observations as to the effects of Turkish baths we cite a pathological case of excessive perspiration. Marischler (1898) describes the case of a boy of 14 who since the age of 8 years had perspired profusely at all times, especially in cold weather. By balance experiments there was found to be a loss of nitrogen, calcium and phosphorus from the body. The nitrogen and phosphorus of the urine were as 100:20 and of the urine and feces together 100:25. Atropin lessened the perspiration, but increased the phosphorus elimination.

Muscle analyses reported by Macleod (1899) furnish some evidence as to the chemistry of muscular activity, in particular with regard to Siegfried's theory as to the value of the nucleon of muscle. Macleod compared the distribution of the phosphorus in the muscles of the legs of dogs that had been exercised in a treadmill for several hours before being killed with that in the corresponding muscles of dogs that had been resting at least twelve hours before being killed. Determinations were made of the moisture, total phosphorus, phosphorus soluble in water, inorganic phosphorus in the water extract, and the phosphorus and nitrogen of the iron-nucleon precipitate. From these values were also computed the organic phosphorus of the water extract, and the portion of this organic phosphorus which was not in the form of nucleon. The results did not support the theory so far as the nucleon is concerned. There was a large loss of the organic phosphorus of the water extract, but less from the nucleon than from the other portion. The inorganic phosphates of the water extract showed corresponding increase, making it appear that some organic phosphorus compound, by its decomposition, plays an important part in muscle metabolism during exercise. It is to be noted also that the total phosphorus of the muscle apparently increased during the exercise by an increase in the compounds not soluble in water. (See tables on p. 468).

Macleod now interprets these results (1914, personal interview) as due first to a formation of lactic acid, and second to a decomposition, by this acid, of organic phosphorus compounds.

FORMS OF PHOSPHORUS IN MUSCLES OF DOGS AFTER RESTING

Number	Age	100 gm. dry muscle contain: A	B	C	D	E	F	G	H	The relation of the most important values to one another			
		Total P	Water extract			Water insoluble P (A-B)	Nucleon		Organic P in water extract minus nucleon P (D-F)	Water-soluble P: total P B/A	Water-insoluble P: total P E/A	Organic P: inorganic P in water extract D/E	Organic P of water extract minus nucleon P: nucleon P H/F
			Total P	Inorganic P	Organic P (B-C)		P	N					
1	2 yr.	0.359	0.238	0.188	0.049	0.121	0.026	0.113	0.023	1:1.50	1:2.9	1:3.9	1:1.1
2	7 yr.	0.362	0.267	0.219	0.048	0.095	0.036	0.057	0.012	1:1.35	1:3.8	1:4.5	1:3.
3	1½ yr.	0.420	0.299	0.235	0.064	0.121	0.029	0.051	0.035	1.1.40	1:3.4	1:3.6	1:0.82
4	3 yr.	0.419	0.304	0.216	0.098	0.088	0.038	0.057	0.060	1:1.37	1:4.7	1:2.2	1:0.63
5	7 yr.	0.367	0.297	0.210	0.087	0.070	0.043	0.072	0.044	1:1 27	1:5.2	1:2.4	1:1.0
6 [1]	9 yr.	0.352	0.247	0.184	0.063	0.085	0.029	0.044	0.034	1:1.34	1:3.9	1:2.9	1:0.82
Mean		0.376	0.275	0.208	0.068	0.097	0.033	0.066	0.034	1:1.36	1:3.98	1:3	1:1

(1) Worked 20 mins. in treadmill, and gave out with dyspnoea; killed and examined at once, no *rigor mortis*.

FORMS OF PHOSPHORUS IN MUSCLES OF DOGS AFTER WORK

Number	Age	100 gm. dry muscle contain: A	B	C	D	E	F	G	H	The relation of the most important values to one another			
		Total P	Water extract			Water insoluble P (A-B)	Nucleon		Organic P in water extract minus nucleon P (D-F)	Water-soluble P: total P B/A	Water-insoluble P: total P E/A	Organic P: inorganic P in water extract D/E	Organic P of water extract minus nucleon P: nucleon P H/F
			Total P	Inorganic P	Organic P (B-C)		P	N					
1	4 yr.	0.432	0.270	0.233	0.037	0.162	0.034	0.044	0.003	1:1.60	1:2.6	1:6.3	1:1.2
2	6 mos.	0.483	0.292	0.250	0.042	0.191	0.032	0.063	0.010	1:1.64	1:2.5	1:5.9	1:3.9
3	6½ mos.	0.481	0.284	0.264	0.020	0.197	0.015	.....	0.005	1:1.69	1:2.4	1:13.2	1:4
4	4 yr.	0.380	0.266	0.223	0.043	0.120	0.017	0.063	0.026	1:1.42	1:3.1	1:5.2	1:0.65
Mean		0.444	0.278	0.242	0.035	0.166	0.024	0.056	0.011	1:1.6	1:2.6	1:7	1:2.1

I. Kaup (1902) concluded that there was no increased protein metabolism because of exertion. There were no food phosphorus figures. The author states that moderate exercise even resulted in phosphorus retention.

Maillard (1908a, 1908b, 1909) studied urinary phosphorus elimination by ten soldiers during 6 days, on an ordinary mixed diet, the object being to determine the effects of muscular exercise and the use of wine. No effects of the use of wine could be noted, on the nitrogen and phosphorus elimination; but the exercise, which was arranged to increase in severity from day to day, in two three-day experiments, caused an undoubted increase in phosphorus elimination in the urine. The total acidity of the urine increased, as well as the undetermined nitrogen, and also to a slight extent the uric acid; while the urea decreased a little, and the ammonia nitrogen, purin bases, nitrogen precipitable by silico-tungstic acid, and total nitrogen were unchanged. The following figures show the effects of exercise on phosphorus elimination in the urine.

Exercise	1st day Light	2nd day Medium	3rd day Severe	4th day Light	5th day Medium	6th day Severe
P_2O_5	1.76	1.72	2.54	1.91	2.25	2.52
P:N	1:48.4	43.3	33.1	44.4	35.4	33.4

Scaffidi (1910-11) studied purin metabolism as affected by the fatigue of mountain climbing. A portion of his phosphorus figures follow:

DAILY PHOSPHORUS BALANCES AS AFFECTED BY FATIGUE OF CLIMBING HIGH MOUNTAINS—Grams

Day	Intake P_2O_5	Urine P_2O_5	Feces P_2O_5	Urine and feces P_2O_5	Balance P_2O_5	Balance N
1	3.634	2.29	0.58	2.87	+0.764	+2.45
2	"	2.42	0.37	2.79	+0.844	+3.149
3 Fatigue	"	2.712	0.96	3.67	−0.036	−2.001
4	"	2.938	0.48	3.41	+0.224	+2.039
5	"	2.75	0.34	3.09	+0.544	+1.089
6	"	2.54				
1	2.70	1.900	0.48	2.38	+0.32	+2.055
2	"	1.593	0.34	1.93	+0.77	+4.525
3 Fatigue	2.363	0.919	0.672	1.839	+0.40	+2.190
4	2.70	1.995	1.37	2.93	−0.23	+3.155
5	"	1.870	0.725	2.31	+0.39	+3.915
1	3.237	1.89	0.78	2.67	+0.567	+2.019
2	"	1.84	0.24	2.08	+1.157	+5.069
3	"	2.62	0.25	2.87	+0.367	+3.239
4 Fatigue	"	2.328	0.75	3.078	+0.159	+4.439
5	"	2.88	1.25	4.23	−0.993	+3.489
6	"	2.14	0.64	2.78	+0.457	+3.219

Scaffidi concluded that during muscular activity there is no increase of uric acid elimination, though there is a slight increase of purin base elimination; also as follows:

Immediately after ending the muscular work, there is a more or less pronounced, but always quickly developing and very evident increase in the amount of uric acid eliminated. During the same time the purin base elimination falls. The increase of uric acid elimination is more pronounced if the work, and especially the rest following, is not taken at too high an altitude.

The total purin nitrogen always rises on the working day; often this increase continues also for two days following the work. This increase is due almost entirely to the increased formation of uric acid, which, as may be concluded from the phosphorus content, comes also from purin bases which result from a tearing down of nucleoproteids.

The elimination of phosphorus rises considerably above the normal mean on the working days and on the following days.

The total elimination of nitrogen is not much changed from that of the resting days, if one leaves out of account the cases when the work undertaken was too great, because of lack of previous training, or because it was carried to excessive duration or intensity.

The ammonia content of the urine, and still more the acidity, rise in consequence of labor.

See also Hammond (1863) and Lepine and Jacquin (1879).

Summary. Ordinary activity does not cause appreciable increase in phosphorus outgo, nor does more vigorous exercise of a man in training. Severe exercise, however, carried to the point of tissue destruction, and this is by no means a rare condition in the lives of many people, may cause marked increase in the outgo of phosphorus, uric acid and other tissue katabolites. The principal part of the increased phosphorus outgo occurs after the termination of the exercise, and the supernormal outgo may persist during several days. The phosphorus outgo is not increased by sweating or massage.

The increased phosphorus outgo after severe exertion is without doubt due to tissue destruction, the muscles probably contributing at least the principal part.

PHOSPHORUS METABOLISM DURING PREGNANCY

Hugounenq (1899a) studied the retention of minerals by the human fetus. The retention of minerals by the fetus is slight at first, but very active at the end. At birth the infant contains about 100 gm. of salts. During the last three months of gestation the fetus acquires twice as much mineral matter as previously.

Ver Eecke (1900) studied metabolism as affected by pregnancy in rabbits. There was in each of 16 cases a very marked decrease in phosphorus elimination during the last week of pregnancy, to a figure usually below that for the period of sexual inactivity, or for the first week of pregnancy. Between the first and last weeks of pregnancy, that is, during the gestation period, the phosphorus excretion was, in twelve cases out of 16, higher than during either the first or the last week. The author connects the decrease in phosphorus outgo with increase in activity of the mammary glands.

Jägerroos (1902), studying nitrogen metabolism in pregnancy, with dogs, reaches the conclusion that in this condition there is a marked tendency toward parallelism in nitrogen and phosphorus metabolism, as is natural, considering the fact that the pregnant female is in a sense a growing animal, and also that there is usually, in the first half of the pregnancy, a period of increased protein decomposition.

Michel (1899) shows the increasing demand of the developing human fetus for phosphorus. The figures are to be found on p. 110.

Schkarin (1910) fed female dogs on various diets, vegetable and animal, and determined the total phosphorus of the pups at birth, and after suckling for varying lengths of time. The effects of the maternal diet on the composition of the unborn young were not pronounced.

Hoffström (1910) studied metabolism of a woman during pregnancy, the subject receiving an ordinary mixed diet. Among the author's conclusions are the following:

1. The phosphorus excreted through the urine was less during the second half of the period than the first, and during this time was comparatively constant in amount.

2. The organism exhibits a greater tendency to hold back nitrogen than phosphorus.

3. The average phosphorus storage was 0.331 gm. daily, and the cumulative storage of phosphorus reached 56 gm. at the end of the experiment.

4. Of this amount 18 gm. were deflected to the fetus, and consequently 38 gm. were retained by the mother organism itself. This was calculated according to figures of Michel for phosphorus content of the fetus at different stages of development.

Numerical data from this work are contained in the following table:

DAILY PHOSPHORUS METABOLISM DURING PREGNANCY

Grams

Week of pregnancy	Intake P	Urine P	Feces P	Total outgo P	Balance P	Cumulative retention P	Ratio N:P Intake	Ratio N:P Urine	Ratio N:P Feces
17	2.060	0.955	1.033	1.988	+0.072	0.504	5.8	10.8	0.9
18	2.300	0.886	0.823	1.709	+0.591	4.641	6.5	12.7	1.1
19	2.862	1.178	0.679	1.857	+1.005	11.676	6.1	11.6	1.2
20	2.471	1.099	1.195	2.294	+0.177	12.915	6.4	11.7	1.0
21	2.304	0.991	1.000	1.991	+0.313	15.106	6.5	12.4	1.1
22	2.223	1.006	0.735	1.741	+0.482	18.480	6.5	11.1	1.6
23	2.231	1.067	0.781	1.848	+0.383	21.161	7.1	10.7	1.6
24	1.482	0.774	0.390	1.164	+0.318	23.387	7.0	12.7	1.4
25	1.927	0.851	0.854	1.705	+0.222	24.941	7.1	13.4	1.0
26	1.835	0.653	0.784	1.437	+0.398	27.727	7.0	15.4	1.1
27	1.569	0.763	0.512	1.275	+0.294	29.785	7.0	11.8	1.2
28	1.458	0.854	0.536	1.390	+0.068	30.261	7.3	11.7	1.1
29	1.998	0.907	0.652	1.559	+0.439	33.334	6.9	11.4	1.3
30	1.754	0.935	0.694	1.629	+0.125	34.209	7.3	10.4	1.3
31	2.136	0.966	0.779	1.745	+0.391	36.946	6.5	9.8	1.2
32	1.892	0.895	0.620	1.515	+0.377	39.585	7.1	10.8	1.2
33	1.834	0.903	0.677	1.580	+0.254	41.363	6.2	10.5	1.3
34	1.909	0.845	0.574	1.419	+0.490	44.793	6.3	9.8	1.5
35	1.994	0.898	0.523	1.421	+0.573	48.804	6.0	9.2	1.5
36	1.670	0.919	0.623	1.542	+0.128	49.700	6.7	9.7	1.6
37	1.957	0.962	0.607	1.569	+0.388	52.416	6.1	9.2	1.5
38	1.972	0.936	0.635	1.571	+0.401	55.223	6.4	9.6	1.9
39	1.872	0.947	0.710	1.657	+0.215	56.728	7.2	11.5	1.7
40	1.149	0.832	0.467	1.299	−0.150	55.828	6.2	9.3	1.3
Mean	1.952	0.918	0.703	1.621	+0.331		6.6	11.1	1.3

See also Mosler (1853).

The extent of the general anabolic excess during pregnancy is indicated by the work of E. Landsberg (1912), who found in human pregnancy a retention of nitrogen four times as great, and of sulphur and phosphorus twice as great, as that required for the fetus.

E. and J. Hermann (1912) reported a study of the lipoid content of the blood of normal and pregnant women, and of new-born infants. The phosphatid content is found about the same for the three bloods, though the proportion of the total fat varies, because both cholesterin esters and neutral fat are high in the blood of the pregnant woman, and low in that of the infant.

SLEEP

Laehr (1890) studied metabolism as affected by sleep, with himself as the subject. He concluded that the calcium, magnesium and phosphorus outgo were not influenced by sleep.

Breisacher (1891) determined phosphorus and nitrogen in the urine in three 8-hour periods per day, during ten consecutive days, in a study of the effects of sleep on metabolism. No figures were given on the composition of the food. Averages of the daily determinations are as follows:

RELATION OF P_2O_5 TO N IN URINE

12-8 A. M. ..... P_2O_5:N=1:5.29
8 A. M.-4 P. M. ..... P_2O_5:N=1:7.46
4 P. M.-12 ..... P_2O_5:N=1:6.93

The subject slept during the period from 12 P. M. to 8 A. M. The author does not come to a definite conclusion as to the reason for the low proportion of nitrogen to phosphorus in the urine formed during sleep. A more rapid elimination of food nitrogen than of food phosphorus would produce such variation in the rate of excretion as the author noted.

Sherman (1902) investigated metabolism as affected by loss of sleep (see table, p. 432), on three successive nights. Increased elimination did not occur until the third day, while changes resulting from alteration of the diet were always perceptible on the first day. There was slight increase in the outgo of nitrogen, sulphur and phosphorus, the proportions not being markedly abnormal.

PHOSPHORUS METABOLISM AS AFFECTED BY THIRST AND WATER DRINKING

Landauer (1894) states that deprivation of water increases both nitrogen and phosphorus outgo, but that after reaching a certain limit the phosphorus elimination returns to the normal.

Straub (1899) investigated metabolism during thirst in dogs. The phosphorus elimination in the urine during periods of 3-4 days without water intake was undoubtedly increased, though only to a slight extent, about 5-10 percent.

In connection with his thorough investigation of the effects of water-drinking on metabolism Hawk (1905) has studied phosphorus metabolism, with results as indicated below.

DAILY PHOSPHORUS BALANCES WITH NORMAL MATURE MEN ON A STANDARD DIET WITH VARYING AMOUNTS OF WATER—Grams

Subject and period	Length of period in days	Initial body weight Kilos	Food P_2O_5	Urine P_2O_5	Feces P_2O_5	Gain or loss P_2O_5	Diet
1—1	2	61.51	5.226	2.340	2.39	+0.496	Milk 1800 gm., butter 75 gm., crackers 330 gm., water 500 c. c.
1—2	2		5.226	2.650	2.36	+0.216	Same as above plus 4500 c. c. water
1—3	4		5.226	2.310	2.33	+0.588	Same as No. 1
2—1	1		4.960	2.509			Milk 1650 gm., butter 60 gm., crackers 300 gm., water 900 c. c.
2—2	1		"	2.754			Standard, same as above
2—3	1		"	2.406			Standard
2—4	1		"	2.568			Standard + 3100 c. c. water
2—5	1		"	2.653			Standard + 3100 c. c. water
2—6	1		"	1.840			Standard
3—1	1		"	2.120			"
3—2	1		"	2.275			"
3—3	1		"	2.330			"
3—4	1		"	2.479			Standard + 3100 c. c. water
3—5	1		"	2.700			" " " " "
3—6	1		"	2.167			Standard
4—1	2	62.8	"	2.925	1.89	+0.145	"
4—2	2		"	3.227	2.20	−0.462	Standard + 3100 c. c. water
5—1	2	61.4	"	2.766	1.92	+0.279	Standard
5—2	2		"	2.943	2.02	−0.003	Standard + 3100 c. c. water
5—3	2		"	2.823	1.93	+0.207	Standard

From this work the author concludes that copious water drinking increases the excretion of phosphorus in the urine, this increase being due to increased cellular activity, and the accompanying katabolism of phosphorus-containing bodies. In every instance the excretion of P_2O_5 was increased above the normal on each day of the water period, the maximum excretion occurring on the second day of the increased ingestion.

From the evidence at hand, then, one must conclude that either great thirst or unusual consumption of water will increase the phosphorus excretion, though further work is required for the positive determination of the source of this phosphorus and, therefore, the significance of this increased outgo.

See also Breed (1851a).

EFFECTS OF TIME OF DAY ON PHOSPHORUS METABOLISM

This is one of those subjects which seems readily explainable on the basis of a few results, but puzzling after the accumulation of an abundance of evidence. A number of extended studies of the question have been made, but there is no such unanimity of findings, or prospect of useful conclusions, as inclines one to attempt to harmonize and summarize the results.

From the papers of W. Kaup (1856b), Haxthausen (1860), Pettenkofer and Voit (1866), Edlefsen (1878, 1881), Speck (1882), Breisacher (1891), Roeske (1897), Vogt (1906) and Sarvonat and Gentz (1911) we conclude that this is a matter which is much influenced by personal idiosyncrasy, environment, and various conditions of the general method of life, such for instance as the time of the chief meal of the day (W. Zuelzer, 1876). We shall mention in detail only two of the later papers.

Sherman and Hawk (1900) studied the urinary elimination by human beings of nitrogen, sulphur and phosphorus as affected by the time of day. As measured by 3-hour periods, the rates of elimination of nitrogen and sulphur run closely parallel, and normally show a tendency to rise during the morning, reaching a maximum after the midday meal, with a slight fall in the following period, and another rise after the evening meal. During the night the excretion usually reaches the minimum.

The excretion of phosphorus describes a curve altogether different from that of nitrogen and sulphates, rising steadily from the middle of the morning until the time of retiring, then falling during the hours of sleep, and continuing to fall for three hours after rising, reaching a minimum after breakfast.

After the ingestion of a considerable amount (63.7 gm.) of extra protein in lean beef with the breakfast, the nitrogen began to rise in the first three hours, the sulphur and phosphorus a little later. The nitrogen excretion regained the normal in 36-39 hours, the sulphur a little earlier, and the phosphorus about 12-15 hours after the ingestion of the beef.

Hawk and Chamberlain (1904) also studied this question with results as below.

VARIATION IN THE COURSE OF PHOSPHATE EXCRETION IN THE URINE AS AFFECTED BY TIME OF DAY AND INCREASED INGESTION OF PROTEIN

Averages of Results from Two Normal Men—Grams

Period	July 16	July 17	July 18	July 19	July 20	July 21	July 22	July 23	July 24
1 6:30 a. m.—9:30 a. m.	0.076	0.086	0.137	0.127	0.191	0.165	0.100	0.194	0.149
2 9:30 a. m.—12:30 p. m.	0.126	0.191	0.254	0.257	0.402	0.317	0.233	0.325	0.276
3 12:30 p. m.—3:30 p. m.	0.302	0.321	0.411	0.422	0.509	0.432	0.383	0.427	0.409
4 3:30 p. m.—6:30 p. m.	0.229	0.243	0.308	0.330	0.409	0.337	0.383	0.351	0.349
5 6:30 p. m.—9:30 p. m.	0.264	0.329	0.399	0.339	0.411	0.390	0.366	0.431	0.335
6 9:30 p. m.—6:30 a. m.	0.747	0.882	0.876	0.881	1.098	1.007	0.909	0.850	0.880
7 Total for day	1.745	2.050	2.387	2.358	3.022	2.702	2.375	2.580	2.402

Average initial weight of subjects, 56.14 kg.; diet, crackers 100 gm., butter 20 gm., whole milk 550 gm. per meal; 3 meals per day, except on July 20, when the morning meal was changed to crackers 50 gm., butter 20 gm., milk 450 gm., and lean beef 100 gm.

In the excretion of phosphorus in the urine two distinct rises were seen each day. The maximum rate was reached after the midday meal. The rate of excretion reached the minimum during the first period in the morning. The maximum rate of phosphate excretion, due to the ingestion of meat in the morning meal, fell in a period between those in which the maxima of nitrogen and sulphate occurred, that is, after the nitrogen maximum and before the sulphate maximum. With one subject the normal rate of nitrogen and phosphate excretion was regained on the second day following the increased proteid ingestion; the normal rate of sulphate excretion was regained one day later, i. e., three days after the ingestion. With the other subjects the normal rate of excretion was not regained in any case until the fourth day following the increase in proteid food.

PART V

PHOSPHORUS METABOLISM IN DISEASE

ACID INTOXICATION

The phenomenon of acidosis is a general condition rather than a specific disease, and is a symptom in many disorders of nutrition. The immediate cause is a disturbance of the phosphate-carbonate balance in the blood which constitutes its central agency for the maintenance of that approximate neutrality which is necessary to the function of respiration.

Having to do especially with compounds other than those of phosphorus, we shall but briefly consider this important matter, and for a fuller discussion the reader is referred to vonNoorden's Metabolism and Practical Medicine.

The general subject of acid intoxication was opened up by the experiments on acid poisoning with animals by F. Walter (1877). Acidosis as relating to human nutrition, however, has to do particularly with acid products of disordered metabolism, rather than with acid poisons introduced from without, and this field of learning was developed after Stadelman (1883) discovered β-oxybutyric acid, and demonstrated the fact that diabetic coma is at least largely due to this compound.

In general, excess of acid in the system may be brought about in two ways, first by actual excess of acid products, and second by such a deficiency of bases as leaves the organism subject to disturbance by a relative excess of the normal acid products of katabolism, the one being in effect quite as truly an acid excess as the other.

The acids of the body which may enter into the disturbance of its approximate neutrality are of diverse origin. They may be (1) inorganic acids from outside the body, (2) unoxidized organic products of acid reaction, (3) acid salts, and acid ions of dissociated neutral salts, and (4) sulphuric and phosphoric acids resulting from protein katabolism; while relative excess of acids may come about (1) through abnormally low intake of alkalis and alkaline earths, (2) through excessive outgo of these same elements, and (3) through deficiency of intake in mineral matter generally, for even a neutral salt may serve for acid neutralization through its anion entering into relations which mask its potential acidity, as for instance with proteins, thus freeing its cation.

The acids actually involved in the production of acidosis as we know it in practice are principally β-oxybutyric and related compounds, in actual acid excess, and the sulphuric and phosphoric acids of normal katabolism, in relative excess of acids.

The reasons are somewhat obscure for the failure of the body, in acidosis, to oxidize β-oxybutyric acid in the normal manner, and for its consequent appearance along with the derived diacetic acid and acetone in the urine. They appear, however, to be either deficiency of carbohydrates, as in starvation and fever, or defective powers of oxidation of carbohydrates, as in diabetes; the coincident oxidation of carbohydrates apparently being necessary to the normal oxidation of β-oxybutyric as well as other fatty acids.

Actual acidity of the blood in the living animal, however, is impossible. These acids do not circulate free, but are neutralized for the protection of the organism. Normally the alkalis used for the neutralization of the acid products of katabolism are furnished principally (1) by the oxidation of organic salts of the fixed alkalis and alkaline earths in the food (especially among herbivora), (2) by the separation of acid urine from alkaline blood, (3) by metabolic ammonia deflected from urea formation (especially among omnivora and carnivora), (4) also to a less extent by carbonates and ammonia in the food, and (5) by ammonia split off from proteins in the alimentary tract by bacteria.

The automatically variable agency for the compensation of varying amounts of acid in the system is the above-mentioned deflection, for acid neutralization, of a part of the ammonia normally contributed by the tissues to the blood as carbamate, and synthesized to urea in the liver, the acids thus forming ammonium salts, and appearing as such in the urine. The amount of ammonia thus rendered available for acid neutralization is quite considerable (omnivora and carnivora), but at the same time it is not unlimited, and the protection afforded is not perfect, even as far as it goes, since the ammonium salts themselves become somewhat toxic through ionization (Wilbur, 1904).

Our usual measure of acid excess in the system, then, however produced, and of whatever nature, is the ammonia of the urine (that is, total ammonia—free NH_3 and NH_3 in salts), though an actual estimation of the disturbing compounds in the blood, as well as the estimation of the inorganic elements of the excreta, afford us supplementary information.

In brief, the effects of acidosis are dyspnoea, and attendant nervous symptoms, terminating in stupor and collapse, the causes being the expulsion of carbon dioxide from the blood by stronger acids, its accumulation in the tissues, and the resultant interference with their oxygenation.

Herbivora and carnivora differ greatly, as Walter showed, as to their resourcefulness in adjusting themselves to excess of acids. In herbivora the food normally furnishes a superabundance of alkali, and therefore these animals have neither need nor capacity for the extensive use of ammonia in acid-neutralization which is characteristic of flesh-eating animals. Acid poisoning, therefore, causes a much greater increase in the excretion of fixed bases by herbivora than by omnivora and carnivora.

So far as known the prevalence of acidosis as differentiated from calcium starvation in domestic animals has not yet been demonstrated.

In human beings acidosis is well known in a great variety of diseases and conditions, especially in diabetes, gastrointestinal disorders in children, fever, starvation, pregnancy, burns and anaesthesia.

Taylor (1904) made a study of human metabolism on an ash-free diet. Metabolism was disturbed apparently by sulphuric and phosphoric acids of metabolic origin.

VonNoorden (1907) states that the blood, muscles and glands give up no appreciable amounts of alkali in diabetic acidosis, but that there is, at the same time, a loss from the body, apparently from the bones, of calcium, magnesium and phosphorus. By subsequent work of many other investigators these facts are well established.

In gastrointestinal disorders of children there is an acidosis which was explained by the work of Keller, Steinitz and Freund. Keller (1897) found an increased elimination of ammonia in the urine always accompanying an increase in the fat of the food. Steinitz (1903) showed that this increased ammonia excretion was due to an acidosis caused by a withdrawal of alkali from the body in soaps formed from fats in the intestine, and excreted in the feces. W. Freund's (1905) observations make it apparent that the increased soaps in the feces are calcium soaps, a part of the calcium normally excreted as calcium phosphate uniting with the fatty acids to form soaps, leaving an equivalent amount of the phosphorus to unite with alkalis and ammonia, the urinary excretion of which is thereby increased.

VonJaksch (1885) first showed that the acidosis of fever is of the acetone variety. The acetone bodies, β-oxybutyric acid, diacetic acid and acetone, are much less abundant in fever than in diabetes, and also less abundant than in complete inanition.

In general, considering the causes and degrees of acidosis in fevers, the quantitative excretion of the acetone bodies is controlled much more directly by inanition, fat destruction, the seat of the infection, and the individuality of the patient than by the temperature, or by the severity of the infection.

As bearing on the effects of experimentally produced dyspnoea on phosphorus elimination, Saccone (1907) found that restriction of respiration in a dog, by the application of a Sayre corset, caused an increase in urinary phosphorus which disappeared after two days.

We may consider, then, that the connection of acid intoxication with phosphorus metabolism is through the participation of phosphates in the maintenance of neutrality; through the contribution of phosphoric acid to the total acids of the body; through the interference of abnormal amounts of acid with synthesis and retention of phosphorus compounds, especially in the bones; and otherwise in still more general ways.

A few references to articles which we have consulted on acid intoxication are the following: Allard (1907); Ewing (1908); Folin (1907); Nichols (1908); Rossi, F., : Inner Respiration of Tissues and Its Relation to Death from Hunger and to Acidosis (Bul. Sci. Med., 81, 149-54); Szili (1906); Talbot (1907) and Fitz, Alsberg and Henderson (1907).

ACROMEGALY

That this disease is due to an excess of function of the hypophysis, or pituitary body, is the prevailing opinion, and one of the more satisfactory investigations in support of this hypothesis is the work of Lewis (Johns Hopkins Hosp. Bul. 16 (1905), 157.), who found, by histological demonstration, hyperplasia of the chromophile cells of the anterior lobe, and other conditions indicative of glandular activity.

Schiff (1897a, 1897b) used hypophysis and thyroid preparations in metabolism studies with acromegalics. The nitrogen and phosphorus of the diets were estimated by calculation, but in the urine and feces were determined by analysis. He found that both the hypophysis and thyroid preparations react strongly on the sluggish

metabolism of acromegalics, producing diuresis, and increased nitrogen and phosphorus excretion, with protracted after-effects, and loss of weight.

Tauszk and Vas (1899) noted retention of phosphorus and loss of calcium in acromegaly, and negative results from the use of pituitary and thyroid tablets.

VonMoraczewski (1901) conducted metabolism studies in acromegaly, with analyses of food, urine and feces, and with blood examination. Hypophysis and thyroid tablets produced no change in the phosphorus retention, which was considerable throughout this experiment. In a second experiment treatment with yohimbine, elemental phosphorus, silver nitrate and oxygen all lessened the retention, or caused a loss of phosphorus.

Oswald (1902), experimenting with a dog, found no definite peculiarities of metabolism following ingestion of powdered pituitary body in quantities of 1-2 gm.

Edsall and Miller (1903) conducted a well-controlled metabolism study of acromegaly. The percentage of retention of phosphorus was 20.88, nitrogen 12.86, and calcium 9.32 in a 7-day period. The phosphorus retention was over a gram a day. The relation of stored calcium and phosphorus shows that the latter could not have been used to any considerable extent in the growth of bone. The subject was an imbecile.

Malcolm (1904) studied metabolism in the dog as affected by the ingestion of pituitary gland substance. The glandular and "nervous" portions of the gland were fed separately in different periods, and in others the whole gland. The calcium and phosphorus balances led the author to the conclusion that the nervous portion is probably the more active and has the effect to cause the katabolism of bone tissue.

Franchini (1904) published results of an experiment in the feeding of hypophysis tablets to a case of acromegaly. This treatment produced nothing decisive in results on phosphorus metabolism.

In a later study (1908b) Franchini published blood analyses from three cases of acromegaly. The data, however, are insufficient to warrant the drawing of conclusions. Still later (1910) Franchini published metabolism and blood data on rabbits and guinea pigs under injection treatment with hypophysis extracts prepared from cattle and horses. These extracts caused a marked loss of calcium and magnesium and a less marked loss of phosphorus. In the circulating blood was found an increase of calcium and magnesium.

Thompson and Johnston (1905) made metabolism studies on dogs under pituitary treatment by ingestion *per os*. The feces were not analyzed for phosphorus. Pituitary substance appears to stimulate metabolism in the dog, as shown by increased outgo of nitrogen (urine and feces), of urea, and to a less degree of urinary phosphates, effects which do not pass away immediately when the feeding of pituitary body is discontinued.

Diesing (1909) expresses the opinion that the hypophysis gland controls phosphorus metabolism, and that its function is physiologically opposite to that of the thyroid in such sense that when the hypophysis stores too much phosphorus, too little connective tissue is formed, leading to myxoedema, or in younger individuals to cretinism, having the same effect as atrophy of the thyroid. When the hypophysis is below normal it causes an excessive growth of bone and connective tissue. The disease acromegaly is the result.

Medigreceanu and Kristeller (1911) injected sterile extract of anterior lobes of hypophysis into an acromegaly patient on two days during a 20-day period of observation. Previous to the first injection the patient was in phosphorus equilibrium. The injection caused a marked loss of phosphorus. Between the first and second injections the organism showed a decided tendency to reëstablish equilibrium, but on the second injection a marked loss of phosphorus was again produced.

See also Delille, (1909).

Mochi (1909) studied elimination of nitrogen, calcium, magnesium and phosphorus in the urine of 8 starving rabbits, of which 6 were treated by injection with extract of fresh lamb hypophysis, one with extract of nerve substance, and one, the control, left without treatment. The author found that, as compared with the control, the animals treated with extract of hypophysis died sooner than the others, but lost less in weight; further, the relation between the nitrogen and phosphorus of the urine showed such an excess of the latter as to indicate destruction of bone tissue. The relation of nitrogen to P_2O_5 in the urine was as follows: Control, 6.5:1; treated with hypophysis, 4.6, 4.3, 4.5, 5.9, 5.3 and 4.5: 1, and treated with extract of nerve substance 8.1:1. (Bibliography of 26 references.)

Mochi (1910) reported further experiments with extract of pituitary body injected into fasting guinea pigs. In complete balance experiments he learned that the increased loss of phosphorus under the pituitary treatment is without doubt due to tearing down of bone tissue. A part of the numerical results are as follows:

AVERAGE DAILY LOSSES OF NITROGEN, PHOSPHORUS AND CALCIUM BY GUINEA PIGS TREATED WITH EXTRACT OF HYPOPHYSIS

Grams

No. of animal	Treatment	Duration of experiment in days	N	P	Ca	Partition of loss of phosphorus	
						From muscle	From bone
I	Fasting only	18	1.6436	0.0934	0.0943		
II	Fasting and injection	17	0.3718	0.1516	0.2776	0.0183	0.1334
III	" " "	16	0.4376	0.1069	0.1571	0.0215	0.0854
IV	" " "	15	1.0127	0.1050	0.1154	0.0498	0.0552

Rubinraut (1912) studied metabolism in acromegaly, and determined that hypophysis ingestion increased calcium and phosphorus elimination, and caused marked loss of these elements, while thyroid therapeutics decreased the rate of elimination of calcium and phosphorus in proportion to the amount of thyroid preparation ingested, the balances becoming positive. Potassium iodide resembled hypophysis in its effects, increasing to a considerable extent both calcium and phosphorus outgo.

Aschner (1912) has made a recent and extensive study of the function of the hypophysis. By extirpation experiments with dogs he obtained results varying in intensity inversely as the age of the animal. In very young dogs the removal of the hypophysis had the effect to retard general development in marked and characteristic ways, affecting the size, hair, claws, teeth, bones, sexual development, etc. These effects were produced by removal of the whole gland, or the frontal lobe, not by removal of the posterior lobe.

Aschner notes the contradictory evidence on results of hypophysis administration, and cites a case of his own, a hypoplastic dwarf in whom there was supposed to be under-functioning of the hypophysis, who under hypophysis treatment increased in height 7 cm. in 5 months.

Aschner cites the work of Benda, M. Sternberg, Erdheim, B. Fischer, v. Frankl-Hochwart, Marburg and others in support of his belief that acromegaly is caused by over-functioning or disordered functioning of the hypophysis, a part of the symptoms being due to its internal secretion, and a part to its local action on surrounding parts of the brain. The true dwarf condition appears to be due, at least largely, to hypo-functioning of the hypophysis, while giantism is rather definitely associated with an excessive functioning of this gland.

The connection, therefore, of this matter with phosphorus metabolism is general in character, but with an especial bearing on the growth of the bones.

ALCOHOLISM

Romeyn (1887) showed that the ingestion of 35-50 c.c. of alcohol by fasting men temporarily decreased urinary phosphorus elimination, an effect which was followed in a few hours, first by an increased elimination, and then soon by a decrease toward the normal for the fasting subject. The increased nitrogen elimination was much less marked.

Saccone (1907) found that alcoholic intoxication reduced the urinary phosphorus in dogs, due perhaps to retarded metabolism.

Salant and Hinkel (1910), experimenting with 4 dogs, found that subacute alcohol intoxication in well-fed dogs causes a moderate diminution of total nitrogen and total sulphur, and a much greater diminution of total and inorganic sulphates and of phosphates in the urine. There is also a tendency to retention of chlorides.

Schittenhelm (1909a) notes that both Pollak and Bloch recognize the fact that in alcoholism, as in gout, there is characteristic delay and diminution of uric acid elimination, and that Landau in extensive studies has come to the conclusion that the elimination of endogenous purins is increased, but that exogenous uric acid is decreased by the loss of ability of the kidneys to let uric acid pass, a phenomenon as yet unexplained.

Schittenhelm conducted experiments with dogs in an effort to clear up this point. Since dogs excrete their purins mostly as allantoin, while men excrete the same as uric acid, it was thought that if there were disturbance in ferment action, which results in slowing up excretion, it would probably show as a change in the end products; and if on the other hand there is a specific injury to the kidney filtration of uric acid, it would hardly hold to the same extent for the more easily soluble allantoin.

Chronic alcoholism was established by feeding meat scrap treated with ethyl and amyl alcohol; and daily urinary nitrogen studies were made both during feeding and fast. As in alcohol experiments with men there was delayed purin elimination, as shown, in this case, by the allantoin. The dog had no appearance of nephritis, and microscopic examination of the kidneys showed no evidence of disease, from which it would appear that there was delayed purin metabolism.

Baskoff (1909b) found that alcohol poisoning reduced the lecithin content of the liver of the dog.

Choumova-Sieber (1910; same as Sieber, 1909a) studied the effects of alcoholism on the organism by the administration of daily doses of alcohol to three dogs during several months. One or two

months after the last dose they were killed, and the organs analyzed for phosphatids. Compared with three control animals they showed a decrease in the phosphatid content of all the organs examined except the kidneys: brain 11.41 percent, mucosa of stomach, 4.15 percent, intestinal mucous membrane 3.22 percent, spleen 3.18 percent, liver 2.74 percent, heart 2.52 percent, lungs 1.34 percent, intestinal wall 1.10 percent, and others. The percentage of decrease was reckoned, not on the phosphatid content of the organs, but on the total dry matter of these parts, and hence the losses noted must be considered as astonishingly large. Examination of the individual records in both groups shows that in almost all cases each of the controls exceeds all of the experimental subjects in the phosphatid content of the organs. This article contains a bibliography of 56 references.

PHOSPHORUS METABOLISM IN ARTHRITIS AND CHRONIC RHEUMATISM

Stokvis (1876), studying phosphorus excretion in arthritis, finds that the urinary phosphorus combined with calcium and magnesium is considerably reduced during the whole of the attack, and that even after the ingestion of lime or magnesia the earthy phosphates remain much reduced in the urine, while in a normal subject increased intake of calcium carbonate or magnesia increases the earthy phosphates of the urine.

Godefroy (1903) finds in the urine, in chronic rheumatism, subnormal amounts both of phosphates and total phosphorus, but on the other hand much more than the normal amount of incompletely oxidized phosphorus.

Joulie (1904) administered phosphoric acid to rheumatic horses in doses of 10 c.c. of the acid (sp. gr. 1.35) diluted to one liter. The excretion of calcium phosphate by the kidneys is said to have been increased.

See also vonNoorden and Belgard (Berliner klin. Wochenschr., 1894).

BERIBERI

Beriberi is a nutritional disorder especially prevalent among the rice-eating peoples of the world, but is not unknown even in America, where it has been found in certain fishing settlements of Labrador in which the people, during several months of the year, live largely on white bread and tea. The disease is characterized by profound nervous disorganization, and appears to be essentially the same as the multiple polyneuritis of fowls.

Volumes have been written to show that beriberi is caused by deficiency of phosphorus in the food; also great works to show that

it is due to poisons of fungous origin. Both of these positions have been generally abandoned, and the problem seems to be at least near to solution, if indeed it is not already solved, on quite another basis. It is, therefore, considered unnecessary to review the earlier literature of the subject.

Prevailing opinion as to the dietetic basis for the disease was set forth by a resolution of the Far Eastern Association of Tropical Medicine after a conference at Manila, in March 1910. The resolution was as follows:

"Resolved, that in the opinion of this Association sufficient evidence has now been produced in support of the view that beriberi is associated with the continuous consumption of white (polished) rice as the staple article of diet, and the Association accordingly desires to bring this matter to the notice of the various governments concerned."

H. Schaumann (1910) has given us an exhaustive treatise on beriberi in relation to the phosphorus of the food, and for a review of the literature up to 1910 the reader is referred to this monograph.

His position at the time of this publication was that beriberi is a metabolism disease which is due to an insufficient supply of organic phosphorus to the tissues, this being caused, in general, by too small a content of organic phosphorus in the food, and in other cases, apparently much less frequently, by insufficient absorption of organic phosphorus compounds when they are supplied in sufficient quantities in the food.

Schaumann considers that scurvy, Barlow's disease, rickets and osteomalacia may have a similar etiology. As indicating some of the details of opinion at that time, and subsequently, we submit the following notes.

Fraser and Stanton (1910) conclude that beriberi is caused by white rice, and that the tendency of rice to cause beriberi varies inversely as the total phosphorus.

De Haan (1910) coincides with these conclusions, and finds that neither lack of salts nor nucleins in the rice is the cause of beriberi.

Highet (1910) agrees in his findings with the above.

Shibayama (1910) considered monotony of diet as a predisposing factor. He believed the disease to be due to a specific organism.

Kilbourne (1910) reported that beriberi varied in prevalence in companies of native Philippine scouts inversely as the phosphorus and potassium of the diet.

Aron (1910a) reported that diets such as cause beriberi contain insufficient phosphorus to maintain health, and that diets similar to those thought to cause beriberi cause polyneuritis in chickens. Experiments with chickens showed that the addition of phytin was of some benefit in this condition.

Aron and Hocson (1910) reported the following balance data:

AVERAGE DAILY PHOSPHORUS AND NITROGEN BALANCES
Periods Four Days Each—Grams

Period and subject	Food	P_2O_5					N	
		Intake	Urine	Feces	Output	Balance	Balance	
a 1-normal	Polished rice, bread, sugar, dried fish, coffee	1.674	1.138	0.526	1.664	+0.01	+0.38	Rice diet
b 1-normal	Same + 75 gm. rice bran, (less bread and rice; more sugar than above)	5.460	1.378	3.460	4.838	+0.62	+0.57	Phosphorus added as rice bran
c 2-normal	Polished rice, bread, sugar, coffee, bacon	1.498	1.735	0.733	2.468	−0.97	−4.67	Lower in N and P than above
d 2-normal	Same + 12 gm. egg albumen, (less sugar, more coffee than above)	1.878	1.568	0.610	2.178	−0.30	−1.98	Protein added to above
e 3-beriberi patient	Same as above + 6 gm. phytin, (more coffee than above)	4.913	1.563	1.845	3.408	+1.50	−2.08	Phosphorus, as phytin, added to above
f 3-beriberi patient	Rice, bread, sugar, coffee, bacon	1.103	1.553	0.730	2.283	−1.18	−2.29	Diet such as supposed to cause beriberi
g 3-beriberi patient	Same as above but with bacon containing less N and P_2O_5	1.045	1.240	0.843	2.083	−1.03	−1.94	Diet such as supposed to cause beriberi
h 3-beriberi patient	Same as above + 6 gm. phytin	3.700	1.313	2.885	4.198	−0.50	−1.81	Phosphorus, as phytin, added to above
i 3-beriberi patient	Same as above but with less bread and coffee	3.638	1.093	3.090	4.183	−0.54	−2.77	Phosphorus, as phytin, added to above
j 3-beriberi patient	Same as above but with more and different bacon	1.013	.0.703	0.655	1.358	−0.35	−1.22	No phosphorus added
k 3-beriberi patient	Same as above + 12 gm. egg albumen, but with less sugar	1.263	0.840	0.790	1.630	−0.37	−2.09	Protein added
l 3-beriberi patient	Rice, bread, sugar, fish	1.908	1.133	0.913	2.045	−0.13	−0.58	Typical Filipino diet; about same as first ration above

From this work some of their conclusions are as follows:

"A diet consisting of bread and rice (both poor in phosphorus), some fat (bacon) and sugar, furnishing 40 calories, 0.15 gm. N and 0.025 gm. P_2O_5 per kilo body weight does not cover the demands of the body for N and P_2O_5, and therefore leads to N and P_2O_5 loss from the body. Addition of protein reduces the N loss of the body and the loss of P_2O_5.

"The addition of phosphorus in the form of phytin prevents a loss of that constituent from the body, and if sufficient of this element is added a storage of phosphorus after a period of phosphorus starvation takes place. The loss of nitrogen from the body is reduced by the addition of phytin, as compared with a corresponding period in which phytin is not given.

"A diet consisting of fish, bread, rice, sugar, etc., furnishing 37 calories, 0.2 gm. N and 0.032 gm. P_2O_5 per kilo of body weight, is sufficient to keep a man in N and P_2O_5 equilibrium.

"The addition of rice bran has a tendency to produce a slight storage of P_2O_5; the rice polish in this respect corresponding to phytin. The phosphorus, both of rice and of phytin, is excreted almost entirely in the feces.

"It is highly probable that living for an extended period on a one-sided almost exclusively vegetable diet, which is characterized by its poverty in phosphorus and in protein, may result in beriberi.

"The process of polishing rice removes a fine skin and the outer layers (bran); this rice bran is rich in phosphorus, especially in its organic soluble form (phytin); the content of phosphorus of the rice is considerably reduced by the removal of the bran.

"Polished rice, poor in phosphorus, may cause beriberi in man if it is the main constituent of the food, but it is harmless if sufficient other nourishment, rich in phosphorus and protein, is taken. The same polished rice causes a polyneuritis in chickens. White bread, a food of similar chemical composition as regards phosphorus and protein, cannot sustain monkeys in normal health if it forms the entire diet.

"The addition of phytin (the organic phosphorus compound of rice bran) considerably reduces the deleterious effects of white rice on chickens."

In connection with their study of rice as the cause of beriberi Aron and Hocson (1911a, 1911b) report the following balance data (see next page) from experiments with healthy men.

The subjects subsisted on diets composed largely of rice of different conditions as to milling. The husked rice contained 0.7-0.8 percent P_2O_5, undermilled rice 0.45-0.60 percent P_2O_5, and overmilled rice 0.15-0.35 percent P_2O_5. In addition to rice the subjects received bread, fish, sugar, bacon, coffee, etc. The results show that an intake of less than 1.65 gm. P_2O_5 per 50 kg. of body weight (0.033 gm. P_2O_5 per kg.) is insufficient to cover the demands of the body for phosphorus. The only cases, Nos. 3, 6, and 11, in which

the balance was positive were those which received unpolished rice, rice bran or phytin. Experiments Nos. 3 and 4 show that the body loses phosphorus on a diet of white rice, and that when this is replaced by red rice, the amount of phosphorus exceeds the demand of the body. When the phosphorus intake was high the excess was excreted almost entirely in the feces.

AVERAGE DAILY PHOSPHORUS METABOLISM WITH HUMAN SUBJECTS ON DIETS COMPOSED PRINCIPALLY OF DIFFERENT SORTS OF RICE—Grams

No. and length of experiment	Subject	Body weight Kilos	Food P_2O_5	Outgo P_2O_5		Balance P_2O_5	P_2O_5 metabolism per 50 kg. body weight	
				Urine	Feces		Intake	Balance
3 4 days	Prisoner C	49.0	3.22	1.03	2.03	+0.16	3.30	+0.16
4 4 days	" "	48.6	1.42	1.04	0.83	—0 45	1.45	—0.45
5 4 days	" B	64.0	1.50	1.74	0.73	—0 97	1.15	—0.80
6 4 days	" "	64.0	4.91	1.56	1.85	+1.50	3.85	+1.20
7 4 days	" "	64.0	1.88	1.57	0.61	—0.30	1.45	—0.30
9 6 days	" D	43.5	1.28	0.80	0.49	—0.01	1.65	—0.01
10 4 days	" A	52.5	1.57	1.14	0.52	+0.01*	1.60	+0.01*
11 4 days	" "	52.5	5.46	1.38	3.46	+0.62	5.20	+0.60
12 3 days	" E	54.0	1.77	1.23	0.76	—0.22	1.65	—0.20
13 3 days	" "	54.0	1.77	1.11	0.73	—0.10	1.65	—0.10
14 3 days	" G	45.9	1.45	0.95	0.58	—0.08	1.60	—0.10

* To harmonize with other data, should be —0.09.

Jebbink (1910) concluded, from dietetic studies, that deficiency of nuclein phosphorus in the ration is responsible for the production of beriberi.

Janin (1910) got sufficient benefit from the administration of organic phosphorus compounds to lead him to believe that deficiency of these in the diet causes beriberi.

Kajiura and Rosenheim (1910), as also Eijkmann, found that barley, fed with rice, relieves symptoms of polyneuritis in poultry, and that this improvement is not due to the alcohol-soluble proteid.

Fujitani (1910) found that the very thin skin of half-hulled rice has the power to protect from polyneuritis, but although its phosphorus was present mostly as phytin, that phytin itself does not produce the same benefit.

Chamberlain, Bloombergh and Kilbourne (1910) found that potassium and phosphorus salts did not cure polyneuritis, and that the idea of deficiency of phosphorus as the cause of beriberi must be abandoned. These authors found polyneuritis curable by a dialyzable substance which could be extracted from rice polish with either cold water or cold alcohol.

Teruuchi (1910) found that phosphorus excretion is not very different in beriberi from the same under normal conditions; further, that the protective principle in unhusked rice and in oats, while not injured by 100° heat, is destroyed by heating to 130°-135°. Teruuchi confirmed the conclusions of Eijkmann, Fraser and Stanton that the neuritis-protecting principle in rice hulls is soluble in warm alcohol, and that it is probably not a phosphorus compound.

Simpson and Edie (1911) report that an exclusive diet of white-flour bread, with pigeons, produced degenerative changes in the peripheral nerves, and death; while a diet of whole-wheat bread resulted in health and gain in weight. These authors cured this disease by the feeding of yeast.

Chamberlain and Vedder (1911) report the multiple polyneuritis of poultry and beriberi as essentially the same. They found that extracts of rice polish, and also of white beans, would cure polyneuritis. Chamberlain (1911) also notes the disappearance of beriberi from the native Philippine scouts with a change of diet.

Bréaudat and Denier (1911) also cured beriberi with rice bran.

Fraser and Stanton (1911a, 1911b) note the fact of the low phosphorus content of rice which causes beriberi, and present a general review of the evidence as to the cause of beriberi. They state that cooking of the unpolished rice under pressure at 120° for two hours destroys that principle which prevents polyneuritis. Attempts to isolate this active principle are described. The protective substance was found to be soluble in 0.3 percent HCl, and in alcohol. Phytin was shown not to be the protective compound.

Cooper and Funk (1911) report that exclusive diets of starch, inulin, cane sugar, and dextrine will cause polyneuritis in poultry; that phytin, edestin, casein, or egg-yolk will not cure the same, but that yeast both prevents and cures polyneuritis. Yeast press juice also cures, as does yeast juice after 24 hours hydrolysis with

20 percent sulphuric acid. Another curative preparation was made from rice polish by solution in alcohol, precipitation by phosphotungstic acid, and decomposition with baryta. This compound was free from phosphorus, carbohydrates and proteins.

Schaumann (1911a) concludes that the protective effect of various preparations such as phytin, yeast-lecithin, pepsin-hydrochloric acid extract of phaseolus, rice-bran-phosphatid, and purified hydrochloric acid extract of rice bran and yeast, is due to the combined presence of organic phosphorus and an "activator," which acts on these compounds in such manner as to render them completely available to the organism.

Chamberlain and Vedder (1912) concluded that beriberi was not due to phosphorus shortage nor to acid intoxication.

Funk (1912a) found that polyneuritis of birds causes a decreased nitrogen and phosphorus content of the brain, and is caused by the lack of a basic alcohol-soluble substance which is necessary to the functioning of the nervous tissues; that the medullary sheath, both within and without the central nervous system, is more or less degenerated, that polyneuritis can be cured by preparations from milk, yeast, and lime juice; that the cure is very rapid, the functioning of the axis cylinder being restored before the regeneration of the medullary sheath is completed.

Edie, Evans, Moore, Simpson and Webster (1912) isolated from yeast an anti-neuritic basic compound which they call "torulin," and with which they plan to conduct experiments relating to beriberi. The approximate percentage composition was C 40.5, H 8.07, N 13.32, O 38.11. Three possible structural formulae are suggested as follows:

$$C_7H_{17}N_2O_5$$
$$C_7H_{16}NO_2(HNO_3)$$
$$N(CH_3)_3C_4H_7O_2(HNO_3)$$

Suzuki, Shamimura and Odake (1912) have isolated a basic compound from rice bran which they believe to be the active principle in the prevention of beriberi. It is an organic compound, soluble in alcohol, insoluble in ether, is precipitated by phosphotungstic acid from solutions acidified by sulphuric acid, and from water solution by tannin. It was isolated in crystalline form as the picrate. This compound they call "orizanine." Of the pure compound obtained from the picrate, 5-10 mg. given *per os* or subcutaneously suffice to cure a pigeon suffering from rice polyneuritis. Similar results were obtained with chickens, mice and dogs. They regard orizanine as an essential nutrient. Dogs fed on meat and

polished rice die in a few weeks with symptoms of starvation. They remain in health if 0.3 gm. of orizanine is added to the daily diet. Judged from their therapeutic action, grains and vegetables in general contain orizanine. Milk, eggs, fish and meat, and their alcoholic extracts were without effect on pigeons suffering from the polished-rice disease. With dogs, however, the alcoholic extract of meat is practically as effective as orizanine in preventing or curing the disease. Details of the chemistry of the compound are given.

Schaumann (1912a) now practically accepts the position and conclusions of Funk and his associates, and expresses his belief, based on experimental observations, that the anti-neuritic extract with which he is working contains a phosphatese, or several such, and suggests that this "activator" serves alike in plant and animal physiology in playing a part in the synthesis of organic phosphorus compounds.

Wieland (1912) fed mice on polished rice, and studied the organic and inorganic phosphorus of their bodies with reference to Schaumann's earlier hypothesis connecting beriberi with insufficiency of certain organic phosphorus compounds in the diet. His results did not sustain the theory.

MacLean (1912b) found a substance in animal tissues which possesses an anti-neuritic capacity. It is soluble in water and in alcohol. It is not a lipoid, but is precipitated by excess of acetone from both its water and alcohol solutions. It contains phosphorus apparently only as an impurity. This substance is likely to be present as an impurity in lecithin as ordinarily prepared, and MacLean suggests that to this fact must be due the variable results from the use of lecithin in beriberi.

Eijkmann (1911) found that the protective principle in rice hulls is effective after peritoneal injection.

Fraser and Stanton (1914) state that a satisfactory measure of the degree of polishing of rice, in relation to the cause of beriberi, is its total phosphorus content. A rice which contains less than 0.4 percent P_2O_5 cannot safely be permitted to form the staple article of a diet for man.

See also Moszkowski (1911), Vedder and Clark (1912), Vedder (1912), Strong and Crowell (1912), Gouzien (1912), Fargier (1912), Hulshoff-Pol (1912), Heiser (1912), Grijns (1912), Yamigawa, Koyana, Midorikawa and Mogi (1912), Onodera, Nakamura and Tateno (1912) and Gregg (1913).

THE BLOOD IN RELATION TO PATHOLOGICAL PHOSPHORUS METABOLISM

A review of the literature of the diseases of the blood, and of the composition of the blood in disease reveals a considerable measure of uncertainty and disagreement in the fragmentary evidence, and comparatively little which is characteristic in the associated phosphorus metabolism, a condition due in part, at least, to the natural variability in the composition of the blood in harmony with the number and diversity of its general service functions.

The bearing of the blood diseases on nuclein metabolism as indicated by uric acid excretion has been discussed somewhat recently by H. Strauss in von Noorden's Metabolism and Practical Medicine, to which we refer the reader. We shall, however, review a portion of the literature of other aspects of the subject.

PHOSPHORUS METABOLISM IN CHLOROSIS AND ANAEMIA

Vannini (1904), in five balance experiments, in a study of chlorosis, found absorption of fats, carbohydrates and proteins normal, and a nitrogen storage in four cases out of five. The observations on the mineral nutrients seem to us neither significant nor characteristic. With calcium, magnesium and phosphorus the positive balances were about as numerous as the negative balances, but the latter slightly exceeded the former in magnitude.

VonMoraczewski (1897c) also conducted balance experiments with 3 cases of chlorosis, and 2 of anaemia from carcinoma. In anaemia there was retention of nitrogen, calcium and phosphorus in both of the cases. In chlorosis there was, in each case, nitrogen retention, but the results with calcium and phosphorus varied with the haemoglobin content of the blood. With 25 percent of the normal haemoglobin there was loss of both calcium and phosphorus; with 40 percent haemoglobin there was retention of calcium and loss of phosphorus; with 60 percent haemoglobin there was retention of both calcium and phosphorus. The addition of sodium chloride and $CaHPO_4$ to the food caused nitrogen economy. VonMoraczewski concluded that anaemia itself causes no protein decomposition.

Stejskal and Erben (1900b) report results of a balance experiment on a fatal case of pernicious anaemia. Absorption from the alimentary tract was poor. The salts in the urine were related, one to another, quantitatively, as in the food; and as to calcium, magnesium and phosphorus the patient was practically in equilibrium. There was a slight storage of nitrogen. The authors stated

the opinion that pernicious anaemia is caused by inanition or auto-intoxication following stomach-intestinal atrophy, or to a disturbance of function of the intestinal mucous coat.

Von Moraczewski (1900b) published results of a study of four cases of pernicious anaemia. He states that the results show, first of all, the impaired power of assimilation of the organism. There is but little loss of nitrogen on nitrogen-poor food, and little storage of nitrogen on adding nitrogen to the food. Oxidation appeared deficient, as in chlorosis, leukaemia and nephritis. The increased calcium outgo indicates katabolism of bone substance. The addition of lime caused a general improvement of symptoms, with decreased nitrogen outgo, and improved oxidation of sulphur compounds. The main characteristics of pernicious anaemia he states as follows:

(1) Increased lime excretion; (2) the small values of the outgo, especially of nitrogen and phosphorus; (3) apathy of the organism; (4) lack of accommodation of the outgo to the intake; and (5) usually increased (relatively) chlorine excretion.

PHOSPHORUS METABOLISM IN LEUKAEMIA

Von Moraczewski (1898b) published balance experiments with one case each of leukaemia and pseudoleukaemia. The following are among his conclusions:

Leukaemia is a nitrogen and phosphorus disease; pseudoleukaemia is a nitrogen disorder. Almost all constituents of the food were found to be retained abnormally in leukaemia, because of a lack of katabolism, more in respect to phosphorus and nitrogen than to chlorine and calcium. In the case of pseudoleukaemia the nitrogen and calcium elimination was impaired to a greater extent than that of the chlorine and phosphorus. With the case of leukaemia the inhalation of oxygen caused an increased calcium and phosphorus outgo. The addition of sodium chlorate and calcium phosphate caused an increase in the nitrogen and phosphorus outgo, and an increase in the red blood corpuscles, with a decrease of leucocytes. The treatment with thyroid tablets was beneficial; elimination was increased and the balances became normal. The retention of phosphorus is noted by the author as being contrary to the theory that leucocytosis should cause phosphorus excretion.

Milroy and Malcolm (1898) observed that in splenomedullary leucocythaemia the pathological condition seemed to consist in a hindrance to the leucocytic breaking-down, as evidenced by an absolute diminution of phosphorus, and a marked relative decrease of

the same in proportion to the total nitrogen in the urine. The alloxuric nitrogen, as a whole, was, relatively to the total nitrogen, increased in leucocythaemia, both the bases and the uric acid apparently participating in this increase.

In a later publication Milroy and Malcolm (1899) presented conclusions from a further study of leucocythaemia. In a case of lymphatic leucocythaemia they found a marked diminution in the absolute amount of phosphorus excreted, and also a relative decrease compared to the amount of nitrogen excreted. The alloxuric excretion (uric acid and bases) was hardly affected.

In a case of medullary leucocythaemia where the number of leucocytes was rapidly falling, the phosphorus excretion was found to have undergone no diminution, while the alloxuric excretion underwent marked diminution, which the authors suggest might be explained by Ehrlich's theory of leucocythaemia being a form of active leucocytosis, due to the action of some body circulating in the blood, and acting as a positive chemotactic agent on the myelocytes and fully formed polymorphonuclear leucocytes in the marrow.

White and Hopkins (1899) published urine analyses for two leukaemic patients, in comparison with those from two normal subjects. The feces were not analyzed. They observe, in harmony with von Moraczewski (1898b), the lack of relation between leucocytosis and the excretion of products such as phosphorus and alloxuric bodies, which result from katabolism of nucleins.

Stejskal and Erben (1900a) conducted complete balance experiments with cases of lymphatic and myelogenic leukaemia. In one very anaemic case of chronic lymphatic leukaemia, on a normal mixed diet, there was in a 5-day experiment a marked nitrogen retention, 5.2 gm. per day, indicating, according to the authors, diminished powers of oxidation. Coincident with this nitrogen storage was a retention of 0.17 gm. P_2O_5 and 0.8 gm. chlorine, and a marked loss, 0.35 gm., of calcium. Of magnesium, the output exactly equalled the intake. The authors attribute the loss of calcium to decomposition of bone.

In a case of *leukaemia lienalis et myelogenes,* with the blood in much better condition than in the above case, and with a greater intake of nitrogen, there was a slight loss of this element as well as of phosphorus, while there were slight gains of calcium and magnesium.

According to Balthazard (1901b) an increased lecithin content of the liver is general in diseases involving the destruction of leucocytes.

Y. Henderson and Edwards (1903) studied one case of lymphatic leukaemia during a period of six and a half months. In spite of an enormous leucocytosis (175000-380000 per cu. mm., of which 96 percent were lymphocytes), and in spite of the alternation of periods of great increase and marked diminution in the number of circulating corpuscles, the excretion of phosphorus and of uric acid was at no time excessive. The leucocytosis was considered as due, not to a general increase in nuclein metabolism, but to a failure in the normal destructive processes. During the progress of this study, the phosphorus elimination, which was subnormal at the beginning, decreased to a much smaller figure. The nitrogen, also subnormal at the beginning, also decreased, but not to so great an extent as the phosphorus; so that there was an increase in the proportion of nitrogen to phosphorus in the urine. At the same time the uric acid, which was somewhat above normal at the beginning, increased its proportion to total nitrogen to a considerable extent, and its proportion to phosphorus very greatly, while the absolute uric acid excretion increased slightly. The decreased nitrogen and phosphorus outgo were shown to be due, not to decreased nuclein katabolism, for uric acid excretion increased during the study, but to retention.

Henderson and Edwards harmonize the conflicting observations of Milroy and Malcolm (1898, 1899), who noted decreased phosphorus excretion, and of von Moraczewski (1898b), who noted a marked phosphorus retention, of Magnus-Levy (1898), who recorded a great increase in phosphorus excretion during 40 hours, with slight leucocytosis, and of White and Hopkins, who concluded that there is no necessary proportionality between the number of circulating leucocytes and the excretion of those products (P_2O_5 and alloxuric bodies) which result from the breakdown of nucleins, by showing that these apparent differences are probably due to these experimenters having made their observations at different stages in the progress of the disease, as made clear by the changes in amount and proportion of urinary constituents during their own much more protracted observations.

Symmers (1904-5a) found the excretion of organic phosphorus in the urine pronounced in lymphatic leukaemia, there being a marked change in the ratios of organic phosphorus, both to total phosphorus and to nitrogen, while the ratios of nitrogen to inorganic and total phosphorus showed little if any departure from the normal; and Erben (1908) found in leukaemia that the plasma was normal, but the erythrocytes were low in iron and potassium, and high in sodium, chlorine, total phosphorus and lecithin.

PHOSPHORUS METABOLISM AS AFFECTED BY BLOOD DISSOLUTION

Kühnau (1896-7) experimented on a considerable number of dogs by subcutaneous and intraperitoneal injections of various poisons and foreign substances as follows: pyrogallic acid, blood of a dog poisoned by pyrogallic acid, blood of a normal dog, red blood corpuscles from normal dog blood suspended in physiological salt solution, magnesium sulphate plasma of a pyrogallic-acid-poisoned dog, serum of a pyrogallic-acid-poisoned dog, normal dog's blood serum, normal human blood serum, typhoid serum, leukaemia serum, NaCl solution of haemoglobin, sodium indoxylsulphate, cinnabar and pure carbon. Among the author's conclusions are the following: In blood dissolution there occur considerable leucocytosis, and the following changes in metabolism; (a) an increased excretion of uric acid and purin bases, (b) a rise at the beginning, in the excretion of phosphoric acid, with considerable diminution following it, (c) an increased excretion of chlorine, and (d) chlorine and phosphoric acid excretion stand in an inverse relation to each other, in that increased excretion of the one corresponds to retention of the other.

PHOSPHORUS OF THE BLOOD AS AFFECTED BY BLOOD DISEASES

Anaemia. Von Moraczewski (1896) observed that in lead colic and anaemia the blood relations are identical, and the urine also shows the same similarity. In these cases there was an increase of chlorine and decrease of phosphorus in the blood, and in the urine a decrease of chlorine and increase of phosphorus, especially the alkaline earth phosphates.

Masing (1911a) made a comparison of the blood of rabbits and geese, in a normal state, with the same after the production of an anaemic condition by bleeding, and by injection of phenylhydrazine. In rabbit serum both the total and lipoid phosphorus were increased by the production of an anaemic condition, thus differing from chlorosis, as observed by Erben (1902); and in the erythrocytes the proportions of total, lipoid and nuclein phosphorus to total nitrogen were increased by the production of anaemia. In the goose blood similar results were obtained. The increase in the lipoid and nuclein phosphorus of the corpuscles is regarded as evidence of the youth of these cells.

Chlorosis. Erben (1902) reported analyses of the blood of three chlorotics. He found the lecithin content of the serum low, as also the phosphorus of the ash of the serum, pointing to a decomposition of erythrocytes. There was an increase above normal in the calcium and magnesium of the serum. In the erythrocytes

the fat and lecithin, as well as the ash constituents, were above normal; the cholesterin subnormal; while the iron is decreased in proportion to haemoglobin. Considering the blood as a whole, the protein, lecithin, cholesterin, phosphorus, potassium and iron were subnormal, while the fat, calcium and magnesium were above normal.

Leukaemia. E. Freund and Obermayer (1891) report an analysis of leukaemic blood, and compare it with analyses of normal blood by Jarisch, Schmidt, and Becquerel and Rodier. A part of the figures are as follows:

COMPARISON OF COMPOSITION OF ASH OF LEUKAEMIC AND NORMAL BLOOD

	Leukaemic (Freund and Obermayer)	Normal (Jarisch)
P_2O_5	16.92	8.82
SO_3	12.31	7.11
Cl	17.82	30.74
K_2O	15.65	26.55
Na_2O	38.52	24.11
CaO	0.47	0.90
MgO	0.07	0.53
Fe_2O_3	2.24	8.16
	104.00	106.92
O equivalent to Cl	4.00	6.92
	100.00	100.00

Erben (1908) also reports a case of leukaemia in which the lecithin and total phosphorus of the erythrocytes were in excess of the normal.

PHOSPHORUS OF THE BLOOD AS AFFECTED BY VARIOUS DISEASES

Erben reported analyses of the blood and also of the serum and erythrocytes in a number of pathological conditions. Data from his articles of 1902, 1903, 1905, 1907 and 1908 are included in the table on the following page.

Von Moraczewski (1896) published extensive series of blood and urine analyses of patients with pneumonia, nephritis, syphilis and other diseases. In one case of pneumonia there was in the blood a subnormal chlorine content, followed by an increase after the crisis, and a high phosphorus content due to leucocytosis. See table on page 499.

Peritz (1908) studied the relation of lecithin to lues, tabes and paralysis. In the first contribution, figures were reported for the ether-soluble phosphorus in the feces of cases of tabes and taboparalysis as affected by injections of lecithin. The results are of doubtful significance.

HUMAN BLOOD AS AFFECTED BY VARIOUS DISEASES

Portion of blood	Diagnosis	Parts per 1000 of substance				Percent of ash		
		Lecithin Grams	P_2O_5 Grams	CaO Grams	MgO Grams	P_2O_5	CaO	MgO
Whole blood	Healthy man	2.193	0.292	0.135	0.077			
" "	Chlorosis I	1.769	0.206	0.257	0.049	2.46	3.08	0.59
" "	Chlorosis II	1.715	0.228	0.238	0.055	2.33	2.43	0.56
" "	Chlorosis III	1.668				8.82	0.90	0.53
" "	Nephritis, subchronic parenchymatous	3.545	0.476	0.219	0.033	5.83	2.68	0.40
" "	Nephritis, chronic parenchymatous	1.455	0.477	0.180	0.043	6.11	2.30	0.55
" "	Same with secondary shrunken kidneys	2.421	0.341	0.175	0.025	4.12	2.11	0.30
" "	Granular atrophy of the kidneys	1.226	0.120	0.117	0.012	7.31	1.58	0.16
" "	Nephritis, chronic parenchymatous,* shrunken kidneys, uremia, hypertrophy of the heart	1.452	0.247	0.145	0.024	3.17	1.86	0.31
" "	Diabetes mellitus	0.964						
" "	Leukaemia	5.800	0.764	0.165	0.060	8.64	1.87	0.68
Blood serum	Chlorosis I	1.536	0.093	0.355	0.054	1.14	4.09	0.66
"	Chlorosis II	1.601	0.144	0.247	0.065	1.63	2.79	0.74
" "	Nephritis, subchronic parenchymatous	5.232	0.100	0.357	0.008	1.26	4.48	0.10
" "	Nephritis, chronic parenchymatous	2.251	0.130	0.359	0.005	1.52	4.21	0.06
" "	Same with secondary shrunken kidneys	2.387	0.219	0.232	0.006	2.68	2.83	0.07
" "	Granular atrophy of the kidneys	1.060	0.095	0.156	0.009	1.18	1.94	0.11
" "	Chronic uremia, secondary shrunken kidneys	1.822	0.277	0.177	0.056	3.26	2.02	0.66
" "	Nephritis, chronic parenchymatous*	0.805	0.097	0.185	0.077	1.18	2.25	0.08
Erythrocytes	Healthy man	2.391	0.460	0.067	0.113			
"	Chlorosis I	2.97	0.57	0.01	0.03			
"	Chlorosis II	2.15	0.53	0.21	0.02			
"	Diabetes mellitus	0.957						
"	Leukaemia. Mean of 2 analyses	3.163	0.873	0.085	0.063			
Plasma	Healthy man	2.000	0.127	0.202	0.042			
"	Diabetes mellitus	1.780						
"	Leukaemia. Mean of 2 analyses	1.817	0.111	0.164	0.036			

* Also shrunken kidneys, uremia, and hypertrophy of the heart.

In another article (1908-9a) Peritz states that he has found that the feces of patients having tabes or tabo-paralysis were rich in lecithin, while in the normal man the feces contain only a trace or 0.2 to 0.7 gm. per day. There was also an increase in the lecithin of the serum. The lecithin content of the serum in tabes and paralysis is given as 4.7 to 6.15 parts per 1000.

In a third article, of about the same date as the above, Peritz (1908-9b) submits lecithin estimations on the serum of a large number of cases of lues, tabes, paralysis, and other nervous affections. The figures for the same disease vary remarkably. We discover nothing characteristic in them.

Peritz (1910) reported further work of a similar nature. Both ingestion and injection of lecithin in syphilis, tabes, neurasthenia, and the normal state are shown to increase the lecithin in the serum. Lecithin determinations were also made in the fat of the bone marrow of cases of *dementia paralytica*. These figures varied from 0 to 4.21 percent of lecithin in the fat.

CHLORINE AND PHOSPHORUS OF THE BLOOD AND THE URINE AS AFFECTED BY THE CRISIS OF CERTAIN DISEASES

Von Moraczewski (1896) Percent

Disease	Sex	Blood analyses						Urine analyses							
		Chlorine		Phosphorus		Calcium		Chlorine		Total P		Alkali P		P combined with Ca and Mg	
		Before crisis	After crisis	Before crisis	After crisis	Before crisis	After crisis	Before crisis	After crisis	Before crisis	After crisis	Before crisis	After crisis	Before crisis	After crisis
Pneumonia	M	0.242	0.265	.....	.....	Trace	.....	0.0240	.....	0.1185	.....	0.0621	.....	0.0564	.....
"	"	0.298	0.277	0.0312	0.0360	0.0040	Trace	0.2060	0.7580	0.1167	0.6710	0.0584	0.0339	0.0583	0.0332
"	"	0.218	.....	0.0319	.....	Trace	.....	Trace	.....	0.1022	.....	0.0502	.....	0 0519	.....
"	"	0.224	.....	0.0442	.....	"	.....	0.0182	.....	0.0183	.....	0.0056	.....	0.0127	.....
"	"	0.234	.....	0.0316	.....	0.0028	.....	0.0182	.....	0.0677	.....	0.0452	.....	0.0225	.....
"	F	0.276	.....	0.0350	.....	0.0028	.....	0.0303	.....	0.0258	.....	0.0169	.....	0.0085	.....
"	M	0.290	.....	0.0392	.....	0.0144	.....	0.0970	.....	0.1196	.....	0.0700	.....	0.0496	.....
"	"	0.263	0.283	0.0344	0.0368	0.0050	0.003	0.0607	0.3030	0.0642	0.0349	0.0408	0.0282	0.0234	0.0067
Typhoid fever	F	0.243	0.261	0.0252	0.0329	0.0010	0.013	0.4060	0.5160	0.0406	0.0931	0.0227	0.0621	0.0179	0.0310
Nephritis, parenchymatous	M	0.265	.....	0.0260	.....	0.0030	.....	0.2730	.....	0.0875	.....	0.0677	.....	0.0198	.....
Nephritis, interstitial	"	0.244	.....	0.0330	.....	0.0040	.....	0.4670	.....	0.0367	.....	0.0282	.....	0.0085	.....
Lead nephritis, interstitial	"	0.314	.....	0.0199	.....	0.0104	.....	0.2310	.....	0.0338	.....	0.0226	.....	0.0112	.....
" "	"	0.290	.....	0.0345	.....	0.0050	.....	0.3760	.....	0.0452	.....	0.0169	.....	0.0292	.....
" "	"	0.172	.....	0.0370	.....	0.0240	.....	0.1570	.....	.....	.....	.....	.....	.....	.....
Intoxication, saturnine	"	0.238	.....	0.0290	.....	0.0090	.....	0.3030	.....	.....	.....	.....	.....	.....	.....
" "	"	0.279	.....	0.0240	.....	0.0050	.....	0.3040	.....	0.0564	.....	0.0423	.....	0.0141	.....
" " "	"	0.282	.....	0.0259	.....	Trace	.....	0.4550	.....	0.0452	.....	0.0226	.....	0.0226	.....
" " "	"	0.246	.....	0.0370	.....	0.0240	.....	0.2730	.....	0.0564	.....	0.0479	.....	0.0085	.....
Syphilis; Hg. treatment	"	0.236	0.275	0.0340	0.0340	0.0040	Trace	1.0619	0.8490	0.0395	0.0367	0.0282	0.0282	0.0113	0.0085
" " " 10 days	"	0.269	.....	0.0290	.....	Trace	.....	.....	.....	.....	.....	.....	.....	.....	.....
" " " 20 "	"	0.294	.....	0.0265	.....	0.0080	.....	.....	.....	.....	.....	.....	.....	.....	.....
" " " 3 "	"	0.219	.....	0.0308	.....	0.0010	.....	0.9220	.....	0.0931	.....	0.0677	.....	0.0254	.....
" "	F	0.262	0.272	0.0237	0.0292	0.0090	0.004	0.8010	0.7402	0.0987	0.0679	0.0877	0.0341	0.0110	0.0338
" "	"	0.249	0.279	0.0263	0.0340	0.0030	0.009	0.6370	0.6060	0.0846	0.1157	0.0564	0.0847	0.0282	0.0310
Syphilis; Ag. treatment	"	0.280	.....	0.0324	.....	0.0030	.....	0.3340	.....	0.0792	.....	0.0452	.....	0.0340	.....
" " "	"	0.259	0.282	0.0217	0.0246	0.0010	0.001	0.5340	0.5340	0.0847	0.0508	0.0508	0.0145	0.0339	0.0362
Pernicious anaemia	"	0.315	.....	.....	.....	.....	.....	0.4070	.....	0.0525	.....	0.0476	.....	0.0049	.....

Bornstein's (1909) studies of the blood in cases of progressive paralysis give us the following values for the lecithin content of blood serum. Normal serum is said to contain 2.0-2.4 parts lecithin per 1000 parts of serum; and serum from these subjects having progressive paralysis contained 3.5, 2.7, 2.8, 2.8 and 2.7 parts and that from one subject having tabo-paralysis, 2.9 parts per 1000.

Glikin (1909c) determined lecithin in the blood in *polycythaemia rubra megalosplenica,* a disease in which the blood contains an abnormal amount of iron. As compared with Abderhalden's figure of 2-3 gm. lecithin per 1000 c.c. of blood (for mammalia), Glikin's determinations of 5.226 and 5.041 gm. per 1000 c.c. in this disease make it appear twice as high as the normal.

Takemura (1910) determined total phosphorus in the blood serum of cases of syphilis and cancer, and from subjects in the normal state. The averages for syphilis and cancer are both a little higher than for the normal subjects, though there is nothing characteristic in the individual figures.

Kimura and Stepp (1911) note Peritz's finding of a high lecithin content of the blood serum in lues, tabes and paralysis, and at the same time an elimination of lecithin in the feces, from which he concluded that these diseases involve an impoverishment of the body in lecithin. Kimura and Stepp continued this study, and reported ether-soluble phosphorus determinations on the serum of 36 cases of various diseases, with results in grams of lecithin, per 1000 c.c. serum, as follows: High values, pneumonia 2.10, typhoid convalescent 2.0, optic neuritis 2.15, diabetes mellitus 2.36-2.60, lues (spinal) 2.27, tabo-paralysis 1.97; low values, Basedow's disease 0.9, chronic nephritis 0.60-1.1, and cardiac insufficiency with chronic nephritis 0.5.

According to Sawadski (1911), the normal content of blood corpuscles in organic phosphorus is 0.8 per 1000, that of the serum 0.17 per 1000, that of the inorganic phosphorus in the erythrocytes is 0.6-0.7 percent, in serum 0.12-0.14 percent. In diseases which are accompanied by an increased acid content of the blood the amount of inorganic phosphorus increases. In infectious diseases the amount of organic phosphorus of the serum is less; in uraemia both kinds of phosphorus rise. The partition of both the organic and the inorganic phosphorus between serum and erythrocytes is, under normal conditions, 1:5. By pathological processes only the quotient for organic phosphorus changes.

The following are the averages of Pusanow's (1911) analyses of the mineral part of normal blood and that from sufferers from arteriosclerosis.

MINERAL DETERMINATIONS ON BLOOD IN NORMAL AND PATHOLOGICAL CONDITIONS (Pusanow, 1911) Percent

Condition	Number of cases	P_2O_5	SO_3	NaCl	CaO
Normal	28	0.33	0.67	0.80	0.01
Arteriosclerosis	14	0.43	0.85	0.81	0.17

Bürger and Beumer (1913a) found cholesterol and lecithin values in blood serum higher in diabetic lipaemia and cholaemia than in other diseases studied.

LECITHIN THERAPY IN DISEASES OF THE BLOOD

Jolly (1887a) and others have expressed the belief that poverty of the food in phosphorus compounds may contribute, as well as lack of iron, to the cause of anaemia. Whatever the facts in this matter, we have a number of reports of attempts to cure anaemia by phosphorus compound therapy.

Kepinow (1910) found that the lipoids of beef blood injected into rabbits which had been rendered anaemic by bleeding, led to a greatly accelerated renewal of the subject's blood, as compared with controls. The injection of lecithin was not attended by like results.

Tonelli (1898) administered lecithin in cases of anaemia and chloranaemia, and noted increase in body weight and haemoglobin; and in simple anaemia, increase in the number of red blood corpuscles. There was also improvement in general condition and in the digestion.

Muggia (1898) described 3 cases of anaemia and infantile athrepsia which were treated by injection of lecithin and egg yolk. The blood was examined. These treatments are said to have had nutritive and curative value.

F. Levy (1905) reports 5 cases of anaemia which were treated with a lecithin-containing preparation, "lecitogen." This medicament contained a variety of ordinary nutrients, and 0.94 percent of lecithin. A general increase of haemoglobin and erythrocytes was noted in the blood. We could present a long list of common foods containing very much more lecithin than does lecitogen. The improvement in these cases was probably due to other constituents of the preparation, though we should reserve the possibility that lecithin in the free state is absorbed, in larger part as such, than is the phosphorus of combined lecithin, in which case the free lecithin might be more useful in metabolism.

Lewin (1905) reports results of blood and urine examination with 8 patients suffering from chlorosis and secondary anaemia, under treatment with bromlecithin. The 5 cases of chlorosis were said to be pronounced and typical. In all cases there was evident improvement, as shown by increase in haemoglobin and in the number of erythrocytes, as well as in favorable changes in clinical appearance.

Bergell and Braunstein (1905) administered bromlecithin, containing 20 percent bromine, in quantities of 0.2 gram 3 times daily to anaemic patients, with results of moderate increase in haemoglobin and red blood corpuscles. Seven patients were included in this study, aggregating 13 periods of 4 to 28 days. The drugs were administered in pill form.

NUCLEIN THERAPY IN ANAEMIA

Jacob and Bergell (1898) studied metabolism in various diseased conditions as affected by a nuclein preparation from calf spleen. This extract was in the nature of a "beef tea." It contained in 1 c.c., 0.0083 gm. N and 0.0034 gm. P_2O_5. Of the phosphorus 93 percent was organic, 35 percent being nuclein phosphorus.

Carefully conducted balance experiments, preceded by proper preliminary periods, showed in secondary anaemia an increase of leucocytes, during 12 days, from 3,680 to 11,250; and erythrocytes from 4,200,000 to 5,775,000 per cubic millimeter; in pernicious anaemia there was no improvement; in anaemia following parturition the erythrocytes increased during 6 days from 1,450,000 to 2,625,500, the leucocytes remaining constant, while the haemoglobin increased from 20 percent to 31 percent; in anaemia with uterine cancer the erythrocytes did not increase, but the leucocytes increased during 8 days from 3,100 to 6,800; in chlorosis there was an increase during 9 days from 325,000 to 4,100,000 erythrocytes, and at the same time, a decrease from 13,900 to 5,100 leucocytes.

In an experiment with a woman 21 years old, under carefully regulated conditions, the authors found that the nuclein preparation was well absorbed, but that it was without perceptible influence on metabolism.

The authors consider the more striking results of their investigation to be the diuresis caused by spleen extract in secondary anaemia, the thorough absorption of the nuclein phosphorus, the improvement in blood conditions, and the improved phosphorus retention. They recommend the administration of nuclein-containing diet in the treatment of all organisms suffering from a loss of phosphorus.

CALCAREOUS DEGENERATION

Almost nothing on this important subject has come to our attention in which the participation of phosphorus has received mention.

O. Klotz (1905) has studied the process of calcareous degeneration, and concludes that the first step in the process is cloudy swelling, or coagulation necrosis; following this there are fatty changes in the cells; and soaps of sodium, potassium, and presumably ammonium, are to be detected. These soaps combine with calcium salts in solution in the body fluids. Later, judging from the fact that phosphate and carbonate of lime are formed, and the deposits give no reaction for fats, the fatty acid moiety of the calcium soap is replaced by the more powerful phosphoric and carbonic acids.

Barillé (1910) advances the theory that atheromatic deposits of calcareous material are due to decreased oxidation, the reduced amount of carbon dioxide being insufficient to keep the phosphates in solution, in which connection might be mentioned the work of Flesch (1876), who determined that all of the constituents of bone are dissolved from bone powder suspended in water into which carbonic acid was led, the whole being kept at body temperature.

A peculiar pathologic retention of phosphates is described by Vannini (1911) under the name of "kalkgicht." Calcium salts were deposited in quantity beneath the skin. The balances of sulphur and chlorine were negative; other mineral elements, especially the alkaline earths and phosphorus, were stored.

CANCER

The concensus of opinion has it that in cancer the phosphorus of the urine is often, though by no means always, increased, usually coincidently with increased nitrogen elimination, both resulting from tissue destruction. Under circumstances which result in starvation the relative amounts of the urinary constituents show that the bones as well as the soft parts are contributing to the phosphorus excretion. The metabolic effects of cancer are the consequences of its growth, of whatever nature these effects may be as determined by the parts involved, and of the disturbed state of nutrition, especially due to undernourishment. There is, therefore, nothing characteristic in general phosphorus metabolism in cancer.

Among the many investigations of metabolism in cancer the following have to do especially with phosphorus compounds: Müller, F., 1889; von Recklinghausen, 1891; Apolant, 1893; von Moraczewski, 1895b, 1897c; Braunstein, 1903-4; and Takemura, 1910.

Hannes (1906) reports results from the subcutaneous injection of 2-percent sodium nucleate solution in 51 cases of uterine cancer, the same being administered in 50 c.c. quantities 10-16 hours before operation for extirpation of cancer. The author was of the opinion that this treatment increased resistance to infection.

Goodman (1912) finds a nuclease in carcinomatous tissue and considers its possible connection with the malignancy of carcinoma.

Volter (1913) found phosphatid and protein phosphorus lower in carcinomatous liver tissue than in neighboring normal tissue, the nitrogen and fatty acid contents showing no differences.

Robin (1911, 1913a) reports that cancerous portions of the liver contain more inorganic matter, including phosphorus, than healthy portions, the slower the cancerous growth the greater the accumulation of inorganic matter.

Robin (1913b) found that variations in urinary phosphorus in cases of cancer were not characteristic of the disease, but were variable in accord with secondary conditions, especially the amount of food consumed, the extent of the tissue destruction, and the character of the tissues involved. He does not in this latest work find retention of phosphates in cancerous tissue.

CARIES

Mosetig-Moorhof (1885) found no dissolving of bone after the application of lactic acid for the purpose of destroying fungous granulation in a case of *caries fungosa.*

Conrad Cohn (1889) made comparative analyses of normal dentine and such as had been affected by caries. The results make it appear that the changes wrought by the disease are such as to increase the percent of both water and organic matter, while the percent of phosphates and carbonates decreases. The calcium and magnesium phosphates each lose fully two-thirds, and the calcium carbonates about four-tenths. The table gives the mean results of the analyses.

COMPARISON OF THE DENTINE OF NORMAL AND DISEASED TEETH
Cohn (1889)—Percent

Teeth	Water	Organic matter	Lime phosphates	Lime carbonates	Magnesia phosphates
Normal	4.27	28.39	52.902	12.93	1.08
Diseased	10.91	66.38	14.470	7.92	0.35

These figures show a phenomenal increase of organic material and decrease of salts, especially calcium phosphate.

Gassmann (1908) noted that the lime content of wisdom teeth is high, and of the teeth of the dog lower than in man, which may be a reason that man's teeth, and especially the wisdom teeth, yield to caries more easily than the dog's. There is indication also that a high content of organic matter increases the general resistance. The analyses compared are as follows:

COMPARISON OF TEETH WHICH DECAY EASILY WITH THOSE WHICH DO NOT (Gassmann, 1908)—Percent, Fresh Basis

	Human teeth				Teeth of dog
	Canines	Milk teeth	60-year teeth	Wisdom teeth	
				Mean of 2 computed	Mean of 2 computed
Lost on glowing	22.20	22.84	21.42	18.51	26.11
Ca	29.78	29.59	30.25	31.77	27.42
Mg	0.87	0.78	0.82	0.80	0.76
PO_4	40.98	40.64	41.10	41.48	39.07
CO_3	4.18	4.12	4.32	5.17	4.50
Cl	0.41	0.37	0.24	0.40	0.18
K	0.34	0.35	0.27	0.33	0.15
Na	0.61	0.54	0.61	0.67	1.00
Sum	99.37	99.23	99.03	99.13	99.19
Water	8.09	8.76	8.27	6.83	11.03

Gassmann (1910) reports an increased magnesium content of the teeth in caries, and expresses the idea that increase of magnesium in bones bears an essential relation to pathological conditions.

EFFECTS ON PHOSPHORUS METABOLISM OF CASTRATION AND OVARIOTOMY

Pinzani (1898) studied the effects of spaying on the metabolism of a dog. The food was the same before and after the operation. Total nitrogen, urea and phosphoric acid in the urine were decreased, as also was feces nitrogen.

Schulz and Falk (1899) found in metabolism experiments on dogs, before and after spaying, that this operation did not lead to increased phosphorus excretion.

Mossé and Oulié (1899) studied the effects of spaying on phosphorus elimination with dogs. The removal of both ovaries caused a moderate increase in urinary phosphorus. The ingestion of ovaries caused a reduction in the phosphorus outgo. Spaying was without result on the excretion of total nitrogen.

S. Neumann and Vas (1902) studied metabolism in dogs as affected by spaying and by ovarian preparations administered before and after spaying. Complete balance data were obtained. Subcutaneous injection of ovarian preparations, with a normal dog,

caused increased excretion of nitrogen, calcium and phosphorus. After spaying there was increased nitrogen but decreased calcium and phosphorus outgo. The feeding of ovarian preparations to spayed dogs caused increased excretion of calcium and phosphorus, but no important change in nitrogen metabolism.

From the following determinations on the tissue and bones Heymann (1904a, 1904b) concludes that: "I. It is certain that castration of healthy, female animals results in no continued phosphorus retention. 2. A decrease in the phosphorus content of the organism follows castration. 3. This decrease seems to affect the phosphate of the body tissue as well as that of the skeleton. 4. The lecithin content is not affected by castration."

PHOSPHORUS COMPOUNDS OF RATS AS AFFECTED BY OVARIOTOMY
Heymann, (1904a, 1904b)

	Tissues, percents of dry substance				Bones, percent total P_2O_5		Bones and tissues, total P_2O_5
	Lecithin P_2O_5	Nuclein P_2O_5	Phosphate P_2O_5	Total P_2O_5	Fresh substance	Dry substance	Percent of total body weight
Normal.....	0.4760	0.0559	2.4479	2.9798	21.2690	24.0556	1.9819
"	.....	.....	.....	.....	18.1665	22.8105	1.2980
"	0.3242	0.0649	1.6490	1.9830*	17.0315	19.2083	?
"	0.3608	0.0979	1.5430	2.0018	17.5724	19.9277	1.3795
41 d. after castration	0.3229	0.0517	1.3671	1.7417	19.3633	22.3595	1.4928
51 d. " "	0.2881	0.1027	1.2147	1.6055	18.9100	22.2174	1.3875
88 d. " "	0.2638	0.0536	0.6616	0.9790	11.5705	13.1568	0.8481
126 d. " "	0.3404	0.0540	.....	.....	14.9766	16.7290	?

* Apparently erroneous since the sum of the figures for nuclein, lecithin and phosphate phosphorus is 2.0381 percent.

McCrudden (1907, 1910a) castrated two dogs, and spayed two, in a study of the effects of these operations on mineral metabolism. Of his results McCrudden says in part, "It will be seen that they do not confirm the view generally held that castration is followed by a general retention of material, especially the mineral elements of the body. In fact, my results show a general tendency in the other direction."

This work was controlled with care. The doubtful trend of the results of these experiments and of those which precede it shows that the facts as to the influence of spaying and castration on phosphorus metabolism can not be markedly characteristic.

See also Daniel-Brunet and Rolland (1911a).

COMPOSITION OF THE HUMAN BODY IN DISEASE

A considerable number of analyses of organs of human beings dead from disease may be found in print, but little is usually made of them, and indeed little can be made of them, for the analyses of the

parts can hardly be expected to afford much of a measure of their functional activity. This most important purpose can be served only by a consideration of the products of the activity of the organs. On this account we have transcribed but few such analyses. Von Moraczewski (1897a), however, has published a very nice series of analyses of the organs of human beings who had died from various diseases, and we copy these and his discussion, practically complete, as an example of the sort of evidence which may be obtained from such studies. This method of investigation of pathology is not entirely without value, but promises comparatively little.

MINERAL CONSTITUENTS IN HUMAN ORGANS AFTER DEATH FROM VARIOUS DISEASES—Percent

Organ	Disease	Dry matter	Nitrogen in fresh substance	Chlorine in fresh substance	Phosphorus in fresh substance	Phosphorus in dry substance	Calcium in fresh substance	Sex
Brain	Pneumonia	30.2	1.159	0.222	0.291	0.97	0.007	M
"	Carcinoma, starvation	14.5	1.356	0.153	0.256	1.76	0.024	F
"	Carcinoma, anaemia	7.15	1.309	0.213	0.280	3.98	0.090	F
"	Pernicious anaemia	18.4	1.942	0.152	0.246	1.33	0.012	F
"	Death by bleeding	21.3	1.944	0.145	0.266	1.25	0.004	M
"	Normal state			0.070			0.002	
Heart	Pneumonia	16.9	2.668	0.142	0.183	1.08	0.004	F
"	Pneumonia	14.0		0.319	0.149	1.02	0.009	M
"	Carcinoma, starvation	12.0	2.703	0.157	0.188	1.57	0.067	F
"	Carcinoma, starvation	13.7	1.821	0.153	0.149	1.09	0.017	M
"	Carcinoma, anaemia	8.8	2.292	0.170	0.124	1.38	0.009	F
"	Carcinoma, anaemia	16.2	2.237	0.142	0.093	0.58	0.001	M
"	Pernicious anaemia	18.1	2.758	0.159	0.160	0.89	0.005	F
"	Pernicious anaemia	21.9	2.295	0.189	0.150	0.68	0.009	M
"	Death by bleeding	15.4	2.319	0.141	0.121	0.90	0.002	M
"	Normal state	36.0		0.070	0.203	0.74	0.007	
Spleen	Pneumnoia	16.6		0.178	0.237	1.42	0.002	F
"	Pneumonia	17.8	4.237	0.335	0.331	1.30	0.001	M
"	Carcinoma, starvation	17.9	2.860	0.215	0.245	1.36	0.015	F
"	Carcinoma, starvation	14.4	2.646	0.176	0.188	1.36	0.003	M
"	Carcinoma, anaemia	13.4	2.464	0.174	0.218	1.61	0.004	F
"	Carcinoma, anaemia	19.2	2.740	0.198	0.259	1.81		M
"	Pernicious anaemia	11.8	2.801	0.259	0.195	1.65	0.010	F
"	Pernicious anaemia	19.5		0.186	0.214	1.09	0.001	M
"	Death by bleeding	8.3	2.350	0.140	0.266	2.14	0.004	M
"	Normal state			0.011	0.132		0.077	
Liver	Pneumonia	34.1	4.071	0.092	0.189	0.55	0.001	F
"	Pneumonia	11.7	1.584	0.271	0.932	7.99	0.004	M
"	Carcinoma, starvation	17.2	2.701	0.191	0.216	1.25	0.017	F
"	Carcinoma, starvation	28.6	2.022	0.184	0.180	0.62	0.001	M
"	Carcinoma, anaemia	38.6	2.712	0.174	0.199	0.51	0.004	F
"	Carcinoma, anaemia	17.4	2.561	0.153	0.237	1.35	0.001	M
"	Pernicious anaemia	9.1	3.285	0.216	0.154	1.69	0.003	F
"	Pernicious anaemia	17.2	2.565	0.125	0.217	1.25	0.017	M
"	Death by bleeding	4.3	2.945	0.209	0.099	2.30	0.012	M
"	Normal state			0.027	0.388		0.028	
Kidney	Pneumonia	9.4	2.293	0.188	0.181	1.92	0.003	F
"	Pneumonia	12.2	2.155	0.392	0.156	1.28	0.004	M
"	Carcinoma, starvation	12.8	2.291	0.167	0.131	1.04	0.012	M
"	Carcinoma, anaemia	3.5	1.913	0.218	0.178	5.05	0.003	F
"	Carcinoma, anaemia	16.7	1.793	0.038	0.214	1.22	0.001	M
"	Pernicious anaemia	10.4	2.404	0.263	0.153	1.47	0.008	F
"	Pernicious anaemia	11.8	1.933	0.255	0.166	1.35	0.009	M
"	Death by bleeding	9.8	2.421	0.136	0.161	1.64	0.003	M
Lungs	Pneumonia	12.4	2.734	0.191	0.188	1.51	0.004	F
"	Pneumonia	9.9	1.581	0.246	0.138	1.39	0.005	M
Blood	Pneumonia			0.276	0.035		0.003	F
"	Pneumonia			0.242	0.032		0.002	M
"	Anaemia			0.301	0.008		0.005	F
"	Anaemia	6.96	0.995	0.300	0.015	0.21	0.005	M

Discussion by author. "While the phosphorus in the main follows the variations of the nitrogen, it is the opposite with the chlorine and the calcium. The minimum phosphorus content accompanies the maximum chlorine content, while it usually corresponds with the minimum of nitrogen.

"This is true of the relations under different causes of death as well as for the individual organs. Of the organs the brain only is an exception, in that here the chlorine parallels the phosphorus, the nitrogen, on the other hand increases and decreases. In the other organs as well as in the different bodies there is the antagonistic relation of chlorine and phosphorus. I must emphasize that this is true only *for most cases* and it is not the rule throughout, for both parallelisms and irregularities of variations in the series of figures are observed.

"The relation of chlorine to phosphorus seems to me most plain in the direction mentioned. The parallelism between phosphorus and nitrogen is less plain, for one observes not uncommonly that the amount of chlorine runs parallel with the amount of nitrogen rather than the amount of phosphorus. In general in the case of individual organs the phosphorus content corresponds rather to the nitrogen content, on the other hand in the individual bodies the phosphorus and chlorine are proportional to the nitrogen, which can be understood, for there the water content of the organs plays an important part. For the consideration of the relations of the mineral parts with one another, therefore, the series of numbers should be used in which they are arranged according to the organs.

"The calcium is usually present in so small an amount that one cannot form a correct conception as to its relation. It gives the impression that it goes parallel with the chlorine rather than the phosphorus. Here also there is no rule shown.

"There is therefore no clear relation of the mineral parts to one another and to the nitrogen, nor is there any more a difference between the different bodies established. I expected to find a typical relation between the chloride and the phosphorus, as it is so often found in the blood in life. I thought the anaemic body would appear very different from the non-anaemic.

"This is not so. There is, it is true, a chlorine richness of the anaemic body as compared with the non-anaemic, and I will not neglect to emphasize this; but this difference in chlorine content is far less marked than was that in the blood in life.

"Still, one thing is made fairly certain by these analyses: the accumulation of chlorine in the organs and the impoverishment of them in phosphorus and calcium. All known analyses of organs

up to this time, with whatever errors may have been made, agree in showing a low chlorine content—about 0.07% computed to the fresh substance. Our analyses show an average of 0.20%, or about three times as much. The phosphorus content is, according to the different authors, 0.3-0.2%; we found usually less than 0.2%. In normal organs the amount of phosphorus is 3-7 times as great as the amount of chlorine; with our cases it is often smaller than the amount of chlorine and but seldom larger, usually equal. It is especially surprising that in the spleen the phosphorus content seems to be increased and in the liver and muscle, decreased. This signifies that the organs lose chiefly calcium phosphate and retain only nuclein phosphorus. The storage of chlorine is caused by the organism becoming watery. That this is not a general condition of cadavers is shown by the fact that the figure for dry substance usually given never falls below 30%. Our analyses give repeatedly figures that are lower than 20%. The large number of determinations support this number; moreover, it has long been known that the blood may in anaemia contain only 8% dry substance in place of the usual 20%, so that a growing watery condition of the organs is nothing unusual. This high water content carries with it the high salt content. Further, it carries with it that the water-soluble salts are principally represented, therefore chlorides and soluble phosphates, not calcium phosphate. C. Schmidt explains the high chlorine content of the blood by the abundance of water in the blood and this theory has in recent times repeatedly been expressed, to explain the retention of chlorine in anaemia and pneumonia.

"There seems to be no doubt that the organs become watery in life in certain diseases. Post mortem analysis has shown this and the high salt content may well be explained in this way.

"In consideration of my former experiments I think I am justified in a further conclusion. I think that the organs in life change under all kinds of disease in the sense that they become richer in water and in salts, but that the blood follows the relationship in the organs only when it itself becomes diseased—therefore only in anaemia. This is the only way to explain why the blood is poor in chlorine in pneumonia though the organism retains chlorine, and why with like chlorine retention by the organism the blood is increased in chlorine content in cases of anaemia.

"The taking up of water is therefore always to be looked upon as a sign of disease in an organ, and with the modern theory of solutions many of the remarkable reactions of the organism may be traced to this '*dilution*'."

Dennstedt and Rumpf (1905) also made an extensive series of analyses of human organs after death from many diseases.

For further observations see discussions of the specific states or diseases of interest.

PHOSPHORUS METABOLISM IN DIABETES MELLITUS

Diabetes is an anomaly of metabolism which results in chronic excess of sugar, especially dextrose, in the urine. This is due to excess of sugar in the blood, resulting from a failure of the liver to convert it into glycogen; as caused either by affection of the glycogenic center in the brain, or, more commonly, by the absence of the internal secretion of the pancreas.

In advanced cases of diabetes there is evident a reduction of oxidative capacity of the body generally, as shown by the appearance of imperfectly oxidized metabolic products, largely of an acid character, in the urine. The acid character of these products is at least largely, though probably not wholly, the cause of the coma in this disease.

In severe cases there is further disturbance of general metabolism through failure of digestion, insufficient intake of food, and excessive destruction of body proteins.

VonNoorden found an excretion of calcium, magnesium, and phosphorus much in excess of the quantity in the food, and of phosphorus much in excess of that which would accompany the excreted nitrogen in the soft tissues; and concluded that this was due to katabolism of bone. A. R. Mandel and Lusk (1904) also found phosphorus elimination excessive in diabetes. VonNoorden cites the work of Gaethgens, showing that when there is no acid-intoxication the excretion of calcium is normal, and the work of Van-Ackeren showing that the bones atrophy as a whole, though vonNoorden is of the opinion that these phenomena are not due simply to the action of an acid. VonNoorden also has shown an increased excretion of purin bodies in such severe diabetes as results in much destruction of tissues. He cites the work of Gaethgens and Külz showing that the natural parallelism between nitrogen and phosphorus of food and excreta usually exists, except where there is acidosis. Under this latter condition the phosphorus excretion, as previously noted, becomes supernormal in comparison with the nitrogen outgo.

Gerhardt and Schlesinger (1899), and also vonNoorden, showed that under these conditions of excessive phosphorus outgo in diabetic acidosis the ingestion of sodium bicarbonate served greatly to reduce this excess excretion of phosphorus in proportion to nitrogen.

Von Moraczewski (1897b) found in one case of diabetes mellitus, on a mixed diet, a retention of nitrogen and chlorine coincident with a loss of calcium and phosphorus, the phosphorus loss being nearly three times as great as the calcium loss. The phosphorus loss was 32 percent of the intake, and the calcium loss 11 percent of the intake. On an animal diet containing much less chlorine and lime, and somewhat less phosphorus, the nitrogen balance remained positive, but the chlorine became negative, and the losses of phosphorus and calcium were increased. Von Moraczewski thought that the lime excretion was a specific symptom, and that decreasing the lime in the food decreased the sugar excretion.

A year later von Moraczewski (1898a) published further balance data on diabetes mellitus. When added to a mixed diet, calcium phosphate (10 gm. per day) seemed to cause a retention of calcium, perhaps a slight increase in nitrogen storage, a reduced loss of phosphorus, and a reduced excretion of sugar, while sodium chloride (10 gm. per day) appeared to have an unfavorable influence on nitrogen, phosphorus and calcium balances. In a later paper (1903-04) von Moraczewski published urine analyses from three cases of diabetes mellitus on various diets. The ingestion of tricalcic phosphate was said again to have reduced the sugar excretion.

That the increased phosphorus elimination in diabetes is not a necessary concomitant of the pathological elimination of sugar is shown by the work of Lépine and Maltet (1902), who found in phloridzin diabetes that an excretion of 53 gm. sugar per liter of urine did not increase either the proportion of phosphorus to urea or the proportion of phosphorus to total inorganic salts in the urine.

Erben (1907) found a decreased lecithin content of the blood in diabetes mellitus, and large amounts of alkalis and calcium. In a later study he found the blood plasma with a normal lecithin content, but the erythrocytes with lecithin content reduced.

As bearing on the connection of the pancreas with diabetes an experiment by Falta and Whitney (1908) on the effects of extirpation of the pancreas on metabolism in the dog is of interest. See table, p. 512.

The extirpation of the pancreas greatly increased the outgo of all the constituents studied, the increase affecting the minerals more than the nitrogen. The endogenous uric acid elimination was also increased. The authors did not consider that any particular tissues, especially, took part in the katabolism, but that there was simply a much exaggerated hunger metabolism.

EXCRETION OF NITROGEN, CALCIUM AND PHOSPHORUS IN THE URINE OF A FASTING DOG BEFORE AND AFTER EXTIRPATION OF THE PANCREAS

Condition	Dates	Length of period Hours	Urine N Grams	P_2O_5 of urine Grams	CaO of urine Grams
Normal; fasting.....	June 5	24	5.353	0.664	0.0175
" "	" 6	24	3.394	0.588	0.0198
" "	" 7	24	3.864	0.639	0.0246
" "	" 8	24	4.208	0.726	0.0366
Pancreas removed; fasting	July 18-19	14	6.700	1.644	0.0124
" " "	" 19-20	24	11.834	1.275	0.1522
" " "	" 20-21	24	11.981	1.672	0.0792
" " "	" 21-22	24	12.012	2.100	0.0885

PHOSPHORUS METABOLISM IN ENDOARTERIITIS

Hirschler and Terray (1905) studied metabolism as affected by endoarteriitis in a patient 53 years old. The data show that bone dust is assimilable by the human being. In this case it appears that the bone dust increased the storage of nitrogen, calcium, phosphorus and magnesium. In this case, as also in these authors' experiment in feeding bone dust to a dog, the ingestion of this substance reduced the urinary phosphorus and increased the feces phosphorus. In this case of endoarteriitis the patient, weighing 67.6-68.8 kg., was not maintained in phosphorus equilibrium on 7.638 gm. P_2O_5 daily in milk, eggs and rolls; but the daily addition of 3 gm. bone dust, containing 38.8 percent P_2O_5, caused an increase of the total phosphorus of the ration to 8.818 gm. P_2O_5 daily, and resulted in storage of this element. The balance data are as follows:

AVERAGE DAILY METABOLISM IN ENDOARTERIITIS—Grams

Period and days	Food P_2O_5	Urine P_2O_5	Feces P_2O_5	Balances				Blood P_2O_5 Percent	Diet
				P_2O_5	N	CaO	MgO		
I 3 days	.....	2.763	1.206	.....	.....	.....	... .	0.0379	Mixed, normal, much meat.
II 3 days	7.638	5.536	3.224	—1.207[1]	—1.49[1]	+1.305[1]	—0.386[1]	0.060	Mostly milk, also eggs and rolls.
III 3 days	8.818	4.580	3.763	+0.475	+1.61	+1.790	+0.240	0.066	Same as above plus 3 gm. bone dust.

(1) The balance figures take into account matter vomited and blood drawn.

FATTY DEGENERATION

As a result of a very great number of investigations, the current belief in regard to the nature and cause of fatty degeneration, so called, is that this condition results from one or the other of

two processes, or from both acting at once: (1) it may be caused by infiltration of fat from outside the tissue, a process which may be either entirely normal, or due to injury to the cells, and which may be either without demonstrable effect on the functional efficiency of the tissue, or which may proceed to such an extent as to cause interference with metabolism, and even the death of the cell nucleus; or (2) it may result from the release of the tissue fats by the autolysis of the proteins with which they are chemically combined, a process which may greatly increase the visible fat without any increase in the amount actually present; or (3) both of these factors may operate simultaneously.

That the lecithin of the tissues does not constitute a source of the fat which becomes demonstrable in the second type of fatty degeneration has been shown by Lusena (1903) and Rubow (1905), who found that the lecithin of cells remains practically normal even in extreme fatty degeneration. See also Krehl (1893).

Lépine (1901) found that some fatty human livers contained as much as 3 percent of lecithin, on the fresh basis (15 percent on the dry basis), and that in such cases the urine contained much more glycerophosphoric acid than normal. He suggests this abundance of incompletely oxidized phosphorus of the urine as an indication of a fatty condition of the liver.

Lépine and Eymonnet made a study of the glycerophosphoric acid of over 100 cases of different diseases. In fatty degeneration of the liver in tuberculosis he found the amount of glycerophosphoric acid in the urine to be 1.0-1.8 percent of the amount of the nitrogen, as compared with 0.15-0.30 in the normal man. See also F. Munk (1908).

Balthazard (1901b) found in a human liver a high lecithin content associated with fatty degeneration, and later made the same observation on goose livers. The amounts of phosphorus in the goose livers differed rather widely, however, a fact which Balthazard thinks is probably due to their being taken at different stages of the fattening process, which he thinks occasions first a surcharging of the liver with lecithin, and second a replacement of the lecithin with fat, this latter process being accompanied by an excessive elimination of glycerophosphoric acid in the urine (Lépine).

Balthazard (1901a) considered that the lecithin content of the liver increased in a number of pathological states, tuberculosis, diphtheria, phosphorus poisoning, experimental typhus intoxication, inanition and uremia. The determinations of the normal lecithin content of the liver of the various animals involved were not shown to be adequate in number.

Balthazard thinks that a large part of the hepatic lecithins comes from the destruction of leucocytes of the circulating blood.

Satta and Fasiani (1910) conducted autolysis experiments with liver which are not without interest in this connection. They found that the addition of lipoids increased autolysis of the liver, as measured by the amount of nitrogen which passed into solution in a given time. This action is most pronounced if the liver of a starved animal is used for the autolysis.

A vast extent of evidence is at hand on the fatty degeneration of phosphorus poisoning, many hundreds of investigations on this one subject, but its value in assisting us to an understanding of other conditions is not sufficient to warrant us in undertaking the great labor of its organization. We are obliged, therefore, as a practical measure, entirely to omit it from this consideration.

PHOSPHORUS METABOLISM IN FEVER

In fever there is generally reduced alkalinity of the blood as a result of the formation of various compounds of acid character, especially the acetone bodies,—acetone, diacetic acid, and β-oxybutyric acid. The first two are oxidation products of the last, and in the disordered oxidation of fever they naturally appear in the order mentioned, and disappear in the reverse order. Their formation is thought to be due to inanition and to fat destruction. Accompanying these acid products of disordered oxidation is an increase in the urinary ammonia. In many fevers retention of chlorine takes place, but not in all, by any means, as for instance in malaria. In convalescence there is usually a negative chlorine balance. In general, the elimination of chlorine in fever seems to be reciprocal to the elimination of phosphorus, though the phosphorus outgo is more variable than the chlorine retention. To what extent the retention of chlorine is necessitated by the phosphorus outgo, in order to maintain the isotonicity of the blood, has not been determined.

Edlefsen (1882) observed that in acute stages of fever the elimination of phosphorus in proportion to nitrogen was subnormal, and explained this as due to retention for the growth of white blood corpuscles.

Rem-Picci and Bernasconi (1894) studied phosphorus excretion in malarial fever. Some of their observations are as follows:

The total phosphorus excreted in 24 hours is frequently above normal. With increase of temperature above normal there occurred an increase in the urine, and at the same time a decrease of urinary phosphorus, even to 5 mg. P_2O_5 per hour, independently of the diet.

There is a post-febrile increase of urinary phosphorus compensating for the febrile decrease. Phosphaturia frequently follows quinine treatment of the fever. There was established, however, no definite influence of the quinine on phosphorus elimination. These results the authors attribute to an inability of the kidneys during fever to excrete the phosphates formed.

Schwartz (1895) made a special study of phosphorus metabolism in pneumonia, in balance experiments covering 4-7 days, with three subjects, beginning in each case before the crisis of the attack, and continuing until 2-3 days after the critical point. Schwartz found in each case a negative phosphorus balance. The phosphorus outgo underwent a marked decrease beginning before and extending through the crisis, and becoming normal soon thereafter. Schwartz says, "The retention of phosphorus belongs in no way to the character of pneumonia; still less to fever diseases in general."

Chlorine was retained during the fever, the outgo increasing suddenly after the crisis. Schwartz observes a general and consistent reciprocal relation between the sodium chloride and the phosphorus of the blood serum in a number of diseases; that is, the higher the sodium chloride, the lower the phosphorus. He believes that this is caused by a disturbance of osmotic pressure through decrease of phosphorus in the tissues, and neither, as does Terray, that the retention of choline is the initiating factor, nor, as does Edlefsen, that the increased phosphorus outgo, after the crisis may be due to leucocytosis, since Limbeck has shown that this is no longer present after the crisis.

Kühnau (1896-7) studied the urine in a case of malaria. On ten consecutive days the phosphorus (P_2O_5) excretion in the urine was as follows, in grams, 2.131-0.201-1.746-0.231-1.695-0.437-1.876-1.594-2.13 and 1.84. The low figures were from days of fever, when there was, at the same time, an increased excretion of uric acid and purin nitrogen. Kühnau raises the question of the possibility of this being due to the use of phosphates in synthesis by the parasitic organisms. The food of the patient contained 1.50-2.2 gm. P_2O_5 per day.

Von Moraczewski (1896) published many urine analyses from which he concluded that in acute fever diseases there is little chlorine, much sulphur, phosphorus and nitrogen, and an especial increase of phosphate earths, as in anaemia. In diseases where there is fever, the urine shows relatively the same changes as the blood, while in anaemia opposite relations to those in fever exist.

Kalinin (1897) studied urinary phosphorus excretion in three rabbits and a dog during the latent period of fever following inoculation with broth cultures of *B. pyocyaneus* and *B. diphtheriae*. The oxygen consumed, and carbon dioxide excreted were decreased in the latent period; both increased as the fever rose. In the latent period the urinary nitrogen and phosphorus were low, but both increased with rise in temperature, though still subnormal during the first hours of the fever.

Ceconi (1898) also noted that both organic and inorganic phosphorus in the urine decrease in relation to nitrogen in high fever.

Setti (1898) found urinary phosphorus not much altered in broncho-pneumonia.

Hitzig (1898-9) studied urinary excretion in 6 cases of malaria. The hourly excretion in grams of P_2O_5 for these cases on the fever days and the fever-free days are as follows:

Case I	Fever day	0.0167
	Fever-free day	0.0475
Case II	Fever day	0.0060
	Fever-free day	0.0598
Case III	Fever day	0.0016
	Fever-free day	0.0398
Case IV	Small variations for fever- and fever-free-periods	
Case V	Fever day	0.0067
	Fever-free day	0.0234
Case VI	Fever day	0.0042
	Fever-free day	0.0699

The relation of P_2O_5 to nitrogen in the urine was also characteristic, as follows:

	P_2O_5:N Fever	P_2O_5:N After Fever
Case 1	1.60:100	6.4:100
Case 2	0.46:100	8.3:100
Case 3	0.78:100	14.9:100
Case 4	0.58:100	5.7:100
Case 5	2.45:100	5.5:100
Case 6	0.36:100	8.8:100

The total nitrogen and ammonia increased during fever, but the proportion of ammonia nitrogen to total nitrogen increased fivefold. The sodium, potassium and chlorine of the urine greatly increased in fever, the phosphates varying in the other direction, the decrease of the phosphates beginning before the onset of the fever.

Paton, Dunlop and Macadam (1899) studied phosphorus excretion in the urine of female dogs as affected by diphtheria infection (controlled by antitoxin), and by fast. As an average of results from four experiments the authors found a normal daily urinary

excretion of 1.63 gm. P_2O_5, during the fast 1.35 gm., and during fever 1.24 gm. P_2O_5; the percent of P_2O_5 relative to total nitrogen, 21.9 normal, 25.7 in fast, and 17.9 in fever. These figures they consider to show that in fever nuclein compounds are less rapidly decomposed than others containing a lower proportion of nitrogen to phosphorus, or else that katabolic phosphorus is retained.

Von Moraczewski (1899) studied urinary excretion in various febrile conditions. Considering the course of an attack of fever as divisible into six periods, von Moraczewski observed the interrelationship of urinary constituents, and plotted curves to show the initial rise in chlorine and fall in phosphorus, followed by a more protracted fall in chlorine and rise in phosphorus elimination, and then an increase of chlorine and decrease of phosphorus to the normal. Variation in these two constituents was always in the opposite direction.

At a later date von Moraczewski (1902) published observations on a case of acute pneumonia in a man from whom the spleen had been removed, because of tumor, seven months previously. With rise in temperature the white blood corpuscles fell from 70000 to 8000, to rise again when the temperature began to fall, and finally to return to the normal level. With rise of number of white blood corpuscles was associated a parallel decrease in urinary phosphorus from 0.833 to 0.041 gm. P_2O_5 daily, and associated with this, a corresponding decrease of potassium elimination. Calcium, however, varied in the reverse direction. This behavior of the phosphorus excretion is attributed to the increased requirement of phosphoric acid by the increased formation of white corpuscles; while the increased elimination of calcium is perhaps to be explained by an increase in the katabolic processes in the bone marrow associated with the growing number of white corpuscles in the blood.

Von Moraczewski (1900a) conducted 18 nitrogen and mineral balances in simple inflammation of the lungs. The nitrogen loss in fever was found to be dependent on the intake; that is, the greater the intake, the smaller the loss. The chlorine retention was much higher in fever than when the temperature was normal. The calcium outgo was also decreased in fever while the phosphorus balances were usually negative and seemed to follow the nitrogen.

Sommerfeld and Caro (1902) studied metabolism in three children who were convalescent after scarlet fever, with a diet of milk alone. A part of the results are as follows:

AVERAGE DAILY NITROGEN AND PHOSPHORUS BALANCES WITH THREE CHILDREN CONVALESCENT FROM SCARLET FEVER, ON A DIET OF PURE MILK—Grams

Case No. and age	Milk taken C.C.	Nitrogen				Phosphorus			
		Food	Urine	Feces	Balance	Food	Urine	Feces	Balance
I 5½ years	3000	16.395	13.350	0.965	+2.080	3.140	0.663	2.035	+0.442
II 7 years	3700	19.978	15.423	1.058	+3.497	3.875	0.955	2.205	+0.715
III 6 years	2562.5	13.688	12.530	0.535	+0.623	2.688	1.205	1.540	+0.057

Computed from authors' data.

The periods were 4 days each in extent. Cases I and III developed nephritis hemorrhagica in connection with scarlet fever, but recovered, No. I quickly, No. III slowly.

The above experiments were conducted when the patients had been free from fever for several days, but remained in bed. During the balance experiment Case III showed in the urine, leucocytes, red blood corpuscles and kidney epithelium. The phosphorus retention with these children was in Cases I and II quite considerable; in Case III, however, there was a loss of phosphorus with an intake which would normally cause retention even in an adult.

Achard, Laubry and Thomas (1902) studied the question as to whether the retention of chlorine, which occurs in the organism in so marked a degree in the course of certain acute diseases, is accompanied by a retention of phosphates. Daily determinations of chlorine and phosphorus in the urine were made in the different stages of a number of diseases. Then injections of sodium glycerophosphate were made, and the urine examined again. The diseases studied were typhoid fever (7 cases), pleurisy (1 case), pneumonia (5 cases), rheumatism (1 case), pulmonary tuberculosis (1 case), and asystole (3 cases). The authors found no parallelism between the chlorine and phosphates. Increased phosphorus excretion was a frequent occurrence in acute cases of infectious diseases. In typhoid fever it was often greatly increased, and was observed before the chlorine crisis, while there was no general improvement, and while the fever continued. Increased phosphorus excretion occurred even in the period of the acme of certain diseases, as was observed in typhoid fever and infectious icterus, and so can not be looked upon as a forerunner of recovery. This increased phosphorus excretion was often independent of the diet. The injected glycerophosphate was usually quickly eliminated in the urine.

According to Gouraud (1902), the phosphorus elimination is similar in pneumonia and typhoid fever, in absolute value as well as in relation between phosphates and alkalis. The urinary phosphates are diminished in amount during the time when the temperature is at its highest point, and also as long as that temperature lasts. At the beginning of convalescence there is a "phosphate crisis" which varies in intensity according to the disease and its duration. During the fever the percent of phosphate earths in the total phosphates falls from 45 to 30, and sometimes even as low as 10. The phenomenon is reversed at the moment of crisis, which affects especially the earth phosphates, and the percent of phosphate earths in the total phosphates increases to 50 or 60, and sometimes to 70 or 80.

Gouraud (1903) believes that in fever the disintegration of phosphorus-containing compounds is markedly increased, but that the katabolic processes are not carried to the final liberation of inorganic phosphoric acid, the result being such an accumulation of organically combined phosphorus as induces degenerative histological alterations. Urinary phosphates are decreased, the proportion of P to N signifying the seriousness of the malady. In convalescence enzymatic activities become normal and the accumulated organic phosphorus is katabolized and eliminated, the result being a phosphaturic crisis. Death is sometimes preceded by such a rapid disintegration of tissues rich in phosphorus as results in an antemortem phosphaturic crisis the proportion of P to N in the urine becoming above normal.

Garratt (1904) has made an extensive study of metabolism in fever. He is of the opinion that apparent retention of katabolized phosphorus in fever is due to the escape of the phosphorus-rich proteins from the oxidation which overtakes phosphorus-poor proteins, and that increased excretion of phosphorus in fever should be regarded rather as a result of the action of the toxin on tissues rich in phosphorus than of the influence upon these tissues of the pyrexia itself, therefore that it has but little direct connection with the febrile state. This article contains 51 references.

According to Molyakov (1912), sodium nucleate, given in the first stages of scarlet fever, causes a great increase in the number of polynuclear leucocytes.

See also W. Zuelzer (1876) and S. Weber (1901).

Summary. From these notes it is apparent that in fevers the amount of the phosphorus outgo is the resultant of the effects of a considerable number of agencies differing in the nature as well as the degree of their influence, as determined by the cause and duration of the fever, and the state of nutrition of the patient.

Among those conditions making for increased outgo of phosphorus are (1) increased tissue destruction, (2) acidosis and (3) chlorine retention; among those tending to restrict the outgo are (1) decreased intake, and (2) retention for growth of white blood corpuscles and pathogenic organisms. In the post-febrile stages there are unusual tendencies making for phosphorus retention, to compensate for previous losses, but this retention is often masked by an increased outgo due to leukolysis, excretion of metabolic wastes previously delayed by unfavorable conditions, and excretion of products derived from the pathogenic organism. There seem, therefore, to be no invariable rules as to interrelationships of urinary constituents in fevers generally.

GLYCEROPHOSPHATE THERAPY

On account of the facts that lecithin phosphorus is absorbed largely in the condition of glycerophosphoric acid, and that lecithin is exceedingly expensive, considerable interest has attached to the therapeutic use of salts of glycerophosphoric acid.

Pasqualis (1894) found that the calcium glycerophosphate increased the urinary phosphorus a day sooner than did calcium phosphate, but after examination of the blood, concluded that the calcium phosphate was only slightly slower in getting into the circulation. The glycerophosphoric acid was not found unchanged in the urine, even when large amounts were given *per os*, or even by injection. By a new method he finds abundant glycerophosphoric acid in the blood. Pasqualis states that in every organ the glycerophosphoric acid is converted into glycerin and phosphoric acid.

Robin (1895) published urine analyses from several cases of a number of diseases under treatment with sodium glycerophosphate by subcutaneous injection. The author discusses at length, and in detail, various improved conditions of metabolism said to be due to this treatment. In view of the fact that no feces analyses were made we are unable to judge of the validity of the claims.

De Stella (1897) conducted injection and feeding experiments with sodium glycerophosphate on two rabbits and a dog. Urine analysis shows increased excretion of sodium chloride, urea and phosphorus.

Bardet (1900) distinguishes between the therapeutic effects of acid and neutral sodium and calcium glycerophosphates. The acid glycerophosphates can not be used hypodermically. Urinary excretion of phosphates was not appreciably increased by the ingestion of acid glycerophosphates, even when given in large doses. The

acid glycerophosphates increase the titratable acid of the urine. In large doses, 15-25 gm. per day, they have a purgative and chologogue action.

West (1902) reports "immediate and pronounced" results from the administration of sodium and calcium glycerophosphates in 8 cases of neurasthenia.

Street (1902) reports that glycerophosphates are most useful in all cases of nervous impairment due to overwork, or excess of any kind, in premature advance of age, and in senility, attended by general debility; the benefits from their protracted use are said to be striking, and their value considerable in chronic neuralgia, in sciatica (by hypodermic injections along the nerve), and in convalescence from *la grippe*, and acute infectious diseases. Street notes that Magnin of Paris asserts that in diabetes he has seen the sugar remarkably diminished by glycerophosphates. To get the best results it is said to be necessary to administer the glycerophosphates from three to six months, sometimes longer, though occasional interruptions of several weeks in the course of very prolonged administration are beneficial.

Fabiani (1903) reports favorable results from glycerophosphate therapy by oral or subcutaneous introducton in 8 cases.

J. Smolénski (1904) investigated the therapeutic effect of glycerophosphates with 19 infants, one to eleven-and-a-half months of age, and 15 children of one to five years. Both sodium and calcium salts were used. No case showed unfavorable results; many showed improved appetite, and gain in weight.

Novi (1904), in balance experiments on himself, studied phosphorus metabolism as affected by antirabes treatment, with and without accompanying sodium glycerophosphate, taken *per os* or hypodermically. The numerical results are as follows:

AVERAGE DAILY PHOSPHORUS BALANCES WITH A MAN AS AFFECTED BY ANTIRABES, WITH AND WITHOUT SODIUM GLYCEROPHOSPHATE—Grams

Period	Length in days	Intake P_2O_5	Urine P_2O_5	Feces P_2O_5	Balance P_2O_5	Percent of total P_2O_5 ingested			
						Urine	Feces	Total	
1	4	2.4485	1.3345	0.8023	+0.3117	54	32	86	Normal
2	3	2.2827	1.3452	0.9702	—0.0327	59	42	101	Cure, nonvirulent material
3	5	2.1346	1.4573	0.7119	—0.0346	68	33	101	Cure, virulent material
4	5	2.0041	1.4150	0.8190	—0.2300	70	40	110	Cure, virulent, and 0.200 gm. sodium glycerophosphate, *per os*.
5	1	2.3387	1.4858	0.5889	+0.2640	63	25	88	Cure, virulent material
6	3	2.3161	1.4177	0.6581	+0.2403	61	28	89	Cure, virulent, and 0.20 or 0.30 gm. sodium glycerophosphate injected
7	1	2.2335	1.3319	0.5788	+0.3228	59	25	84	Cure, virulent material

The author attributes to the antirabes treatment, both virulent and nonvirulent, a tendency to increase the urinary phosphorus, this being due, Novi thinks, to the same constituent of the injected material, which, while not itself toxic, produces a leucocytosis and a coëxistent or following leucolysis.

The figures show that the administration of sodium glycerophosphate, either hypodermically or *per os*, increased the feces phosphorus, and increased the loss, or decreased the retention, of this element. Ingestion *per os* did not reduce the urinary phosphorus, reckoned as percent of the intake, but hypodermic injection may perhaps have done so to a slight extent.

Frey (1906) has obtained favorable results from therapeutic use of a glycerophosphate preparation containing iron and bromine.

It would seem, therefore, that there is at least similarity in the action of glycerophosphates and lecithin, though the probability is, of course, that the glycerophosphates are less effective through the lack of those functions or superiorities of lecithin which depend on its partial absorption in an unchanged condition.

For an extended review on glycerophosphate therapy see Merck (1911).

PHOSPHORUS METABOLISM IN GOUT

Gout is due to uric acid retention, and results from deranged nuclein metabolism. Observations on phosphorus elimination with nuclein-free and nuclein-containing diets, therefore, have been used in judging of the progress of this disease. Purin base elimination may be even more significant as indicating incomplete formation of uric acid or urea.

Hans Vogt (1901) conducted nitrogen and phosphorus balances with a man suffering from gout, for the purpose of studying nuclein metabolism in this condition. Balance data are below.

AVERAGE DAILY NITROGEN AND PHOSPHORUS BALANCES WITH GOUT PATIENT AND CONTROL AS AFFECTED BY INGESTION OF PANCREAS—Grams

Periods	Gout patient		Control		Body weight of gout patient	Body weight of control	Diet
	N Intake Balance	P Intake Balance	N Intake Balance	P Intake Balance	Kg.	Kg.	
Fore-period 6 days	14.58 +1.16	2.621 −0.513	14.58 −1.76	2.621 −0.938	68.2—68.4	64.3—64.9	White bread, eggs, sirloin steak, butter, cream, beer
Main period 5 days	19.31 +3.79	4.861 +1.016	19.31 +2.01	4.861 +0.865	68.4—68.95	64.9—64.9	Same plus calf's pancreas
After-period 4 days	14.58 −0.33	2.621 −0.535	14.58 −2.38	2.621 −1.108	68.9—68.5	64.9—64.8	Same as first period

The subject suffered from acute gout, caused by beer drinking, and also from kidney trouble. For comparison a second subject was included, a servant ordinarily healthy, but suffering from nervous dyspepsia during this experiment.

The gout patient was 35 years old and formerly healthy. On Apr. 26, 1900, typical symptoms of gout appeared. After treatment with sodium salicylate he showed improvement. The experiment lasted from May 8-May 23, 1900.

Conclusions. 1. There was a nitrogen loss in the preliminary and after periods, due to insufficient intake, but a retention by both subjects during the gland-feeding period.

2. The nuclein is entirely split in the organism. The phosphorus is excreted normally but the nitrogen is retained. This nitrogen retention is not due to a disturbance of the secretory activity of the kidneys, since the phosphorus outgo is normal.

3. Much uric acid was retained by the gout patient in comparison with the control. This is the result of a disturbance of metabolism, which may be due either to a decrease of oxidation or splitting, or to synthetic processes. The outgo of phosphorus as compared with the outgo of nitrogen, and therefore of uric acid, in the case of the gout patient is very small, compared to the control. This points to a tardiness of nuclein metabolism of the gout patient. Whether the large retention of nitrogen is due also to this is not to be concluded from these results.

Waldvogel (1902) reports a metabolism study at the time of a gout attack, in which the urine was examined as to its amount, specific gravity, total nitrogen, uric acid, total phosphorus and disodium phosphate. In conclusion he says, in part:

"The gouty attack may be thus characterized: The nitrogen retention between attacks shows itself to be a slowing up of the elimination of the decomposition products of nucleins, the values for both uric acid and phosphoric acid being small, without any recognizable kidney insufficiency.....

"But while the phosphate shows gradual increase for a long time after reduced nuclein metabolism, the elimination of uric acid rises sharply from the first day of the attack, and it is also increased in the blood bringing about an elevation of δ without kidney insufficiency making its appearance. The uric acid apparently rises from that being produced in the joints, the solution of it in the alkaline blood taking place so rapidly that the kidney secretion cannot immediately make up for the subsequent appearance of uric acid in the blood.

"Also before the attack the relative amount of P_2O_5 and uric acid in the urine is different; on the second day before the attack the amount of uric acid is already low, that of phosphoric acid not. Not till the day before the attack does the value for P_2O_5 fall, while that of uric acid does not appear further reduced."

The data are, in part, as follows:

URIC ACID AND PHOSPHORUS ELIMINATION IN THE URINE OF A GOUT PATIENT FOLLOWING ACUTE ATTACK
Waldvogel (1902)—Grams

Day	Uric acid	Total P_2O_5	Na_2HPO_4	
1	0.652	0.58	0.18	Day of attack
2	0.769	0.71	0.14	
3	0.770	0.61	0.19	
4	0.824	0.74	0.24	
5	0.742	0.81	0.34	
6	0.679	0.88	0.34	
7	0.758	1.48	0.70	
8	0.723	1.43	0.60	
9	0.620	1.25	0.67	
10	0.768	1.57	0.64	
11	0.615	1.37	0.41	
12	0.540	1.21	0.51	
24	0.644	....	....	Two days before a second attack
25	0.479	1.20	0.42	

Kaufmann and Mohr (1902) found that the values of endogenous alloxur nitrogen and the ratio of uric acid-nitrogen to base-nitrogen both fell within normal limits in gouty subjects. They give the following nitrogen and phosphorus balances for 5 gouty persons on nuclein-free diet.

NITROGEN AND PHOSPHORUS BALANCES WITH GOUT PATIENTS ON A NUCLEIN-FREE DIET—Grams

Case No.	Days	Calories intake	Nitrogen		Phosphorus (P_2O_5)		Case
			Intake	Balance	Intake	Balance	
1	4	3200	12.5—13.9	+1.55	....	....	Chronic gout
2	3	?	21.25	+4.72	8.45	+1.16	Chronic gout, "very fat"
3	4	2900	15.65	−2.56	6.25	−0.77	Acute attack
4	3	3200	13.6—19.3	+0.24	6.35—7.35	+0.71	Acute attack
5	8	2350	15.1—16.7	−1.55	5.78—6.33	+0.13	Less acute attack

Judging from the values and the signs of the nitrogen and phosphorus balances, it is supposed that in Case 2 there was a building up, and in Case 3 a breaking down of phosphorized nitrogenous tissue, while in Cases 4 and 5 it appears that the material used was non-phosphorized protein.

These authors also made observations on the absorption and retention of the nitrogen and phosphorus of thymus when added to the purin-free diet, and in one case of chronic gout they added to the diet alternately "dark" (filet) and "light" (veal or haddock) meat; the dark meat gave no greater increase of alloxur bodies than did the light meat.

Ciuffini (1910) compared the calcium, magnesium and phosphorus balances on a normal subject, a subject with chronic gout, and a subject having gout with paroxysms. Balances were noted during 4-day periods on mixed diet and on the same without meat (considered to be purin-free). Urinary phosphorus elimination appeared to be markedly low in chronic gout. In paroxysms there was phosphorus retention before, during and after the highest point of the attack.

Rotky (1910) studied nuclein metabolism in various diseases of human subjects, including gout, and he reports purin nitrogen observations on urine and feces, and P_2O_5 on the urine. Uric acid excretion resulting from a milk diet was considered to be of endogenous origin. Exogenous excretion was studied by means of the addition of guanin, hypoxanthin or thymus to the diet. Serious disturbance of ferment activity was noted in gout, the food purins not being converted to uric acid, and in acute nephritis there was delay of excretion, and but a small part of the purin nitrogen was excreted as uric acid, while urinary purin bases showed a small increase. But slight variation was noticed in the values of phosphoric acid.

With regard to the etiology of gout as an anomaly of purin metabolism the reader is referred to the discussion of Brugsch and Schittenhelm (1910). The discussion includes normal nuclein metabolism, as well as its disturbances, and was preceded by exhaustive investigations on certain phases of the subject (Schittenhelm, 1907; Brugsch and Schittenhelm, 1907a, 1907b, 1907c, 1907d, 1907e, 1907f, 1908-9, 1910; Brugsch, 1909). The reports of others are also extensively quoted.

According to these authors uric acid, originating in nucleins, becomes so abundant in the blood as to exceed its solubility limits in that fluid, and hence urate is deposited in the tissues, which deposit causes the arthritis, pain and fever of gout. The deposits are found to be mainly monosodium urate. Brugsch and Schittenhelm distinguish a metabolic gout and a kidney gout, according as the uricaemia is due to disturbances in the purin metabolism or in the excretion. Disturbance of the kidneys may follow as a secondary result in metabolism gout.

In metabolism gout they find uric acid constantly present in the blood, even on purin-free diet (endogenous uricaemia), and in four-fifths of all the cases which they observed the uric acid excretion, during intervals between attacks, was subnormal or at a low normal value, and the base-N excretion was within normal limits. The ratio of uric acid-N to purin base-N excretion tends toward the lower limit of normal variation. At the time of attack, and immediately afterward, the uric acid elimination was high. The accumulation of exogenous uric acid (exogenous uricaemia) is not considered a retention in the usual sense, but a temporary increase due to a depression and a retardation of urea-formation, from the purin bodies fed, and of the decomposition and elimination of uric acid. According to Brugsch and Schittenhelm this depression and retardation involve the whole fermentative system of uric acid formation and decomposition (especially nuclease and purin deamidase, together with the uricolytic ferment, and to a far less degree the xanthin oxidase). See Miller and Jones (1909) for evidence throwing some doubt on this point.) This weakening of the ferment activity raises the uricaemia to hyperuricaemia, and the symptoms of gout appear.

Of phosphorus metabolism during gout we may say then that in acute attacks the balances may be positive or negative. The phosphorus excretion falls before the attack, is low during the attack, and rises slowly thereafter during a considerable period. In chronic gout the urinary phosphorus excretion is low.

INFLUENCE OF HEMORRHAGE ON PHOSPHORUS METABOLISM

Hawk and Gies (1904) in their work on the influence of external hemorrhage on dogs included determinations of phosphorus balance. The experiments here reported were on two dogs, normal at the beginning of the work, and subjected to anaesthesia, operation and hemorrhage. The blood was let from the saphena. The diet was meat, crackers and bone ash. As a result of the many alterations in the usual course of metabolism blood letting seems slightly to favor phosphorus retention. The excess of ingested over excreted phosphorus was least in the anaesthesia period (Exp. 1, period 3) and greatest in the anaesthesia-operation period (Exp. 1, period 4). Although the results were not very striking, operation and hemorrhage, in most instances, seemed to cause slight retention of phosphorus; etherization favored increased elimination. The anaesthetic used was principally ether, with a very little chloroform at the beginning.

INFLUENCE OF EXTERNAL HEMORRHAGE ON PHOSPHORUS METABOLISM IN THE DOG—Daily Balances—Grams

Exp. and period	Initial weight of animal Kilos	Treatment	Food phosphorus					Phosphorus balance	Days in period
			Meat	Crackers	Lard	Bone ash	Total		
1-1	16.96	Normal	0.557	0.094	0.026	1.779	2.456	+0.045	12
1-2	16.29	Anaesthesia, operation and 1st hemorrhage, 2.93 percent, body weight	0.557	"	"	"	2.456	+0.123	16
1-3	15.81	Anaesthesia alone	0.558	"	"	"	2.457	+0.015	10
1-4	15.44	Anaesthesia and operation, (no hemorrhage)	0.558	"	"	"	2.457	+0.163	13
1-5	15.18	2nd hemorrhage, 3.22 percent, body weight	0.543	"	"	"	2.442	+0.022	21
1-6	13.76	3rd hemorrhage, 3.51 percent, body weight	0.527	"	"	"	2.426	+0.065	7
1-7	13.35	4th hemorrhage, 3.26 percent, body weight	0.527	"	"	"	2.426	−0.180	4
2-1	11.85	Normal	0.440	0.070	0.013	1.423	1.950	−0.030	9
2-2	11.40	Anaesthesia and operation	"	"	"	"	"	−0.025	9
2-3	10.47	Anaesthesia, operation and hemorrhage, 3.11 percent, body weight	"	"	"	"	"	−0.017	5

HOOKWORM

Vannini (1900) conducted balance experiments with human beings under treatment for anaemia from hookworm (*Anchylostoma*). Nothing characteristic was observed in the phosphorus metabolism.

ICTERUS

The connection of icterus (jaundice) with phosphorus metabolism is comparatively slight and indirect. Neither the overloading of the blood with bile, nor the deflection of bile from the intestine, nor yet the injury which sometimes occurs to the liver cells bears directly on phosphorus metabolism in important ways.

Through under-nutrition there is sometimes an increased katabolism of body protein, and hence an increased production and secretion of endogenous uric acid, but only to such extent as is due to the increased tissue destruction. The increased gastric secretion of hydrochloric acid, which is usually present, probably has a demonstrable bearing on phosphorus metabolism, as also the characteristic calcium soap stools.

Phosphorus metabolism in icterus has been studied by Simnitski and Rodoslawow (1902) and by Schilling (1901a). Simnitski and Rodoslawow found urinary phosphorus nearly normal, though often increased, with relative amounts of constituents normal.

Schilling notes that Szydlowski has stated in a dissertation, "Beiträge zur Mikroskopie der Fäces," that in icterus the feces contain no crystals of tricalcic phosphate. Schilling, however, finds that although in this disease the feces do not usually contain many phosphate crystals, when the food has a high phosphorus content they are readily seen. He finds no relation between the fatty-acid content of the feces and the amount of phosphate crystals present.

LECITHIN THERAPY

The use of lecithin as a drug has been, in large part, due to its prominence as a constituent of the brain, and to the established increase of formation of its cleavage products in degenerating nerve tissue. The conception of administering nutriment to the brain, direct, is attractive, and nothing is more natural than that this idea should have been accepted by the ignorant, overworked by the humbug, and stoutly denied by the honest radical. The extreme claims of many advocates of the use of lecithin in therapeutics have tended so strongly to discredit any such element of truth as they may have expressed that it is with reluctance that we attempt to point out the probable facts.

Approaching the task with the assumption of the sincerity of the average man, we have eliminated some of the obviously unreliable claims, have toned down many of the remainder, and have sought to call attention especially to those points on which there is general agreement. With this explanation it seems unlikely that the following reports should require any further discount than is implied in the suggestion that there is more inclination to record and to publish the favorable than the unfavorable results, and we can only speculate as to the number of unfavorable results which have been suppressed.

Baud (1858a, 1858b) reported beneficial effects, in cachexia, from the administration of phosphorized fatty matter extracted from the medulla oblongata of animals.

B. Danielewsky (1895a, 1895b) states that subcutaneous injection of lecithin in dogs increased the number of red corpuscles up to 800,000 to 1,000,000 above normal, and also increased the haemoglobin. This improvement occurred in a few days after the injection, and lasted for some time.

Serono (1897a, 1897b, 1902) conducted subcutaneous injection experiments with specially purified lecithin on a considerable number of pathological human subjects. There resulted gain in appetite, and improvement in general condition, a rapid increase of red

blood corpuscles, and usually increased nitrogen elimination in the urine. Lecithin was found to possess a tonic effect comparable to arsenic, but acting more quickly. Haemoglobin increased very slowly, and only after improvement of general conditions.

Serono considers it better to administer lecithin hypodermically than by ingestion, because of digestive decomposition in the alimentary tract, and would use egg lecithin rather than brain lecithin, because of admixture of the latter with toxic substances, in doses of 20-30 centigrams or more per day.

Magnani (1898) found injections of lecithin helpful during treatment of the eyes, by improving the condition of the cornea, when it had suffered during lowered nutrition of the whole organism.

Muggia (1898) reports nutritive and curative value of lecithin and egg yolk injected in cases of anaemia and infantile athrepsia.

Saint-Aubin (1900) conducted hypodermic injection experiments on five patients, with a solution obtained by filtration of a mixture of vaseline oil and egg yolk, after heating to coagulate nucleins and albuminoids. The treatment led to increase of weight and of urea elimination, due, it is said, to stimulation of cellular multiplication, and in consequence, of activity of the elements. Phosphorus and uric acid outgo were also increased.

Morichau-Beauchant (1901) has made an extended study of lecithin therapy, and reviews experimental work beginning with that of Danielewsky in 1895. From his conclusions we condense the following:

Lecithin administered either subcutaneously or through the stomach stimulates the appetite, and leads to rapid gain in weight. It stimulates growth, and increases the number of red blood corpuscles and the percent of haemoglobin.

It increases urea, total nitrogen elimination, and the coëfficient of utilization of nitrogen, and diminishes uric acid.

In tuberculosis lecithin is of service in the earlier stages, not as a specific, but as an auxiliary. Similarly it may be of value in diabetes through improving general conditions. It also gives good results, as a rule, in anaemias, cachexias and convalescence. In neurasthenia it is especially valuable.

Lecithin is active in doses of 0.2-0.3 gm. *per os* and 0.05-0.10 gm. subcutaneously each day, or every other day. Lecithin is not toxic in any dose. Subcutaneous administration is indicated in gastrointestinal disorders.

Suzor (1901) treated two patients by subcutaneous injection of raw egg yolk in water solution, and obtained stimulation and improvement of general condition.

Iljin (1901) conducted feeding experiments with a laboratory helper, on mixed diets of normal foods, to which brain and egg yolk were added as carriers of organic phosphorus. From this work we have seen only Maly's brief abstract. The organic phosphorus compounds were considered to have promoted nitrogen retention.

Zaky (1901a, 1901b) studied the effects of lecithin ingestion, in doses of 0.3 gm. per day, on urinary elimination. In experiments with three subjects there appeared to be slight increase of total nitrogen and urea, with decrease of uric acid and phosphorus. The changes were so small as to be of doubtful significance unless established by most critical experiment.

Answering Robin's criticism to the effect that egg yolk increases uric acid excretion Zaky says that it is the nuclein and not the lecithin of the egg which increases the uric acid elimination.

Ariès (1902), on the strength of clinical experience, considers lecithin a valuable remedy in all cases where "denutrition" is to be combatted, especially in old age. He speaks of it as a bioplastic and morphogenic agent.

Maillon (1902) made a clinical and physiological study of lecithin by administration of 0.3-0.8 gm. doses in 34 cases of tuberculosis, chlorosis and nervous diseases, basing conclusions principally on an examination of the urine. He found the amounts of phosphoric and glycerophosphoric acids in the urine unchanged by the lecithin treatment. The ingestion of lecithin, however, was of benefit; in some cases it improved the appetite; in chlorosis it caused a constant increase in body weight, but in tuberculosis the increase in weight was irregular. The effect on the urine, if there was any at all, was indirect.

Stassano and Billon (1902a, 1902b, 1902c, 1902d) conducted a series of experiments on the effects of lecithin injection on the blood elements in animals. Lecithin in physiological salt solution injected into the auricular vein of rabbits produced hyperleucocytosis lasting for several days, and an increase in the ratio of mono- to polynuclear forms.

Intraperitoneal injection, with guinea pigs, caused an increase of both forms of leucocytes. In the lecithin exudate the ingestion of the polynuclear forms by the very large mononuclear leucocytes proceeded with a rapidity suggesting that the mononuclear forms, especially, had taken up the lecithin injected, and nourished themselves therewith.

Further intravenous injections, with rabbits, led to a progressive increase of red blood corpuscles after each injection. Tests showed an increased vitality of these cells, as implied by increase of resistance to saline solutions of various strengths. A different reaction of the red corpuscles to stains, implying increased acidity of the nuclear chromatin, was noted.

By experiments with frogs it was determined that, after having grown large and granular at the expense of the lecithin, the mononuclear leucocytes left the blood vessels, and spread into the system. Endothelial cells in their turn retained lecithin, becoming crammed with granulations, and their nuclei showing marked activity.

Courtial (1903) showed that 1-2 gm. of lecithin taken by healthy people produced no notable differences in the composition of the urine; no increase of either phosphorus or uric acid.

Fratta (1904) conducted hypodermic injection experiments on a human being weighing about 70 kg. with marrow, sodium hypophosphite, glycerophosphates, lecithin and *cura antirabica.* Glycerophosphates and lecithin, injected hypodermically in doses of 0.20 gm. daily, increased urinary nitrogen elimination, but decreased the urinary phosphorus excretion. The *cura antirabica* increased both nitrogen and phosphorus elimination.

Heim (1904) describes "bioson" as a protein-iron-lecithin combination and recommends it as a blood building and nerve strengthening preparation. The iron content is 0.24 percent, and the lecithin 1.27 percent. It is, therefore, not nearly so rich in lecithin as many common foods.

Migliaccio (1904) used lecithin injections in cases of anaemia, atrophy and rachitis,—all infants. The results were rapid and sometimes notable gain in weight, notable improvement in the blood, and in gastrointestinal functions. The urinary phosphorus showed increase in all cases.

Silberstein (1904) discusses and recommends phosphorus treatment with "hemaprotagon" tablets, a preparation containing iron from the blood, and unaltered lecithin. Cases of melancholia, tuberculosis and lues are discussed, and the preparation recommended for such cases.

W. Koch (1905a) stated that for the clinical administration of lecithin to the adult, in the pure form, there is at present no good scientific basis. Koch based this view on the fact that, in the ordinary diet, one consumes vastly more lecithin than is recommended by the promoters of the clinical application of lecithin. He

suggests, however, that with the infant the case may be slightly different in that the lecithin content of cow's milk diluted with water may be reduced to a figure very much below that in human milk.

Snowman (1905) gives clinical reports of benefit from the use of sanatogen, especially improved blood conditions in chlorosis, chorea, and tuberculosis.

For suggestions regarding the therapeutic use of lecithin activated by Röntgen rays, radium rays, and by other means see Werner (1905).

Von Oefele (1907) found "bioson" to be utilized in a normal way during health, and in sickness to be utilized more perfectly than other articles of diet.

Errani (1908) treated 10 pathological cases by lecithin injection. He concluded that lecithin promotes and accelerates the normal bioplastic and morphogenetic processes, improves the metabolism and the constitution of the blood, and, in consequence, the general condition of the organism.

Kleinertz (1908) reported several instances of improvement in clinical condition after the use of "biocitin," a lecithin preparation of Altmann, containing 10.7 percent of lecithin.

Sleeswyk (1908) found that the bactericidal action of certain lecithin solutions on typhus bacilli, as reported by Bassenge, was due to their acid reaction, caused in all probability by impurities in the commercial products used.

W. Koch (1909a), in discussing phosphorus compounds as brain foods, calls attention to the facts that, in comparison with other parts of the body, the nervous system does not have a very large amount of total phosphorus, though it has of lecithin; that the amount is not materially less in cases of dementia praecox, but is reduced in general paralysis; that the commercial phosphorus preparations used as drugs (hypophosphites, glycerophosphates, phytin, lecithin) are much less effective for supplying the requirements for growth of the brain than are phosphorus-rich foods, some of them not being taken up by the system, the amount usually recommended of any kind giving very insignificant addition to the amount of phosphorus taken with the daily food, and there being no conclusive evidence that they have any effect on the growth of the brain.

J. and W. Cronheim (1910) made clinical observations on the use of lecithin with 18 cases, all of them undernourished, and most of them tuberculous. The authors conclude that under such conditions lecithin induces remarkable increase of appetite, and consequent gain in weight.

Renshaw and Atkins (1910) studied the bactericidal properties of lecithin and of choline salts. Such a property of lecithin was shown to be at the most very slight, while there was no indication of bactericidal effect of the choline salts.

Buslik and Goldhaber (1911) conducted metabolism experiments with a lecithin-albumin, "glidine." This preparation appeared superior to scraped meat as to digestibility, absorbability and action on intestinal putrefaction; it permitted forced protein storage, and had a favorable effect on the haemoglobin content of the blood of anaemics; in the last respect, however, "ferroglidine" was still more efficient.

Borschim (1911) applied lecithin to the back of a rabbit to determine its effect on iodine absorption. The result was negative. Lecithin has no such effect.

Milkowicz (1911) found that lecithin and cholesterol *in vitro* cause a great increase of phagocytosis of *Staphylococcus* and tubercle bacilli.

An iodine-lecithin-protein preparation is described by Isaac (1911) and C. Neuberg (1911) under the name "iodocitin."

Bain (1912) obtained from the oral administration of lecithin to rabbits marked increase of both red and white corpuscles and of haemoglobin, and the same results from subcutaneous injection. The increase of white corpuscles was chiefly in the mononuclear lymphocytes.

Similar experiments were conducted with phytin. Introduced by mouth, the improvement in blood conditions was slight; introduction by injection produced marked increase in red corpuscles, but less increase of white corpuscles and of haemoglobin than was obtained by the injection of lecithin.

Bain regards lecithin especially as a metabolic stimulus, its effects on the nervous system being secondary to improvement in general state of nutrition.

In our own experience we have found that egg yolk, presumably through its lecithin content, often improves the digestion of milk by infants, but also that infants differ widely in their toleration of egg yolk.

Among other articles on lecithin therapy are those of Coulombe (1901), who presents a historical review up to 1901, with summary and 56 references; Hartenberg (1901), Huchard (1901), Lancereaux and Paulesco (1901), Labbé (1903), Fürst (1903), Grimm (1903), H. C. Wood Jr. (1903), Goliner (1905), G. Landsberg (1906) and Berkley (1908), the above consisting of clinical reports

of the use of lecithin in a great variety of pathological cases characterized, in general, by low state of nutrition, as after wasting diseases, the results in almost all cases reported being marked improvement of general condition.

It would appear from these clinical reports that, in states of impoverishment, lecithin is a valuable aid in the restoration of the organism to normal condition. Claims of stimulation of growth under normal conditions are not so well sustained, and are difficult of adjudication by reason of the fact that the normal state is variable and not definitely definable.

The benefit derived from lecithin treatment is usually spoken of as improvement of the general state of nutrition, especially as evidenced by improved appetite and digestion (which indeed might be accountable for most of the rest), increased weight, red blood corpuscles, haemoglobin, and white blood corpuscles, especially of the mononuclear form. It is said not to be specific in disease, but to be of value in many derangements,—anaemia, cachexias, convalescence, neurasthenia, etc., through the elevation of the general plane of nutrition.

As to the relative efficiency of lecithin administered as a drug and taken in natural foods we have not information sufficient to warrant a positive statement. If lecithin, taken in the pure form, actually has the capacities which it is said to possess, this may be due to the more extensive absorption in an unsplit condition which seems probable when the compound is administered uncombined with nutrients requiring digestive cleavage.

See also notes on lecithin therapy in the discussion of tuberculosis. For an extended review on lecithin therapy see Merck (1912).

MALNUTRITION OF THE BONES OF THE DOMESTIC ANIMALS

The facts of the existence of malnutrition of the bones as a disease of the domestic animals, the dependence of this disorder primarily on deficiencies in the mineral elements of the food, as determined by its nature and by soil and climate, and the ready response of this ailment to improved treatment, either by change of food, use of fertilizers on the pastures, or direct feeding of bone-producing salts, have been demonstrated many times over in a long series of agricultural investigations in which there is such general agreement that individual statement of the results is unnecessary. The following notes suggest some of the kinds of observations to be found in the literature.

According to Moussu and Dollar (1905) osseous cachexia was known in Norway as early as 1660.

Roloff (1866) recognized pregnancy, lactation and digestive disorders as predisposing conditions, and (1869) doubled the calcium and phosphorus content of meadow grass by the use of fertilizers.

E. Voit (1880), experimenting with dogs and pigeons on lime-poor and other diets, produced rachitic conditions by withholding lime. Animals of the larger breeds suffered more acutely from lime deficiency than those of the smaller, slower-growing breeds. The bones were decreased in phosphorus, magnesium and iron as well as calcium, by the calcium starvation.

Nessler (1873) demonstrated the connection of this disorder with the nature of the underlying rocks from which the soil was derived. Stilling and von Mering (1889) produced malnutrition of the bones in a dog by use of a lime-poor diet. Maier (1894) reports this disorder in pigs fed on low-calcium foods. Von Seelhorst, Georgs and Fahrenholtz (1900) showed that the moisture of the soil affected the phosphorus of the forage. Phosphatic slag gave best results as a fertilizer, through increasing the phosphorus of the plants. Lane (1906) discusses this bone disease in army horses, mules and donkeys in South Africa. Dibbelt (1911) found that pups *in utero* developed normally while the mother lived on such a low-calcium diet as caused puerperal osteomalacia.

Schenke (1903) quotes Pott and Dammann in their recommendations of the amounts of precipitated calcium phosphate to feed to farm animals. Pott advises its constant use with young animals; swine for 6 months, colts and calves for the first year.

Dammann advises feeding to a pregnant and milk-giving sheep 12-20 gm., a sow the same, a mare and a cow 30-50 gm. Wherever there is fear of disturbance of normal bone formation, foals and calves may be given 8-15 gm. daily, and pigs and lambs 3-6 gm.

For young fowls Pott advises a teaspoonful of bone meal for each 12-14, for hens 2-3 gm. each.

Under normal conditions such additions are not necessary, but with food poor in calcium or phosphorus they may be needed. Schenke summarizes a large number of investigations on the use of precipitated calcium phosphate for animals.

Dobrowolsku (1911) has found that phosphorized cod-liver oil is fairly efficacious in relieving the experimental malnutrition of the bones which results from the establishment of fistulae in the alimentary tract.

See also the following articles having to do with malnutrition of the bones in domestic animals: Bopp (1838), Haubner (1854, 1867), Nessler (1866-71), H. Bauer (1868), Karmrodt (1867), Stohmann (1869), Tripier (1874), Haubner (1875), C. Voit (1877b), J. Cohnheim (1882), Stutzer (1888), Kellner, Köhler and Barnstein (1894, 1895), Lafevre (1894), Winkler (1891), Bongartz (1894a), Uhlich (1895), Robert (1895), Bonnetät (1903), Moussu and Dollar (1905), Alquier (1905-6), Grandeau (1905), Lewite (1905-8), Klimmer and Schmidt (1906), Ingle (1907, 1908, 1909), Scheunert, Schattke and Loetsch (1911), and Neubauer and Hillkowitz (1912).

We have not considered infectious osteoporosis and "big-head."

MENTAL AND OTHER NERVOUS DISORDERS

In considering the influence of mental diseases on the phosphorus metabolism of the body as a whole, as measured by the excreta, we should bear in mind the facts that the central nervous system is not highly vascular, and not the seat of intense metabolic change, that it contains but a very small part of the total phosphorus of the body, and that violent functional disorders are accompanied by but slight observable change in its chemical composition. There is, therefore, no reason to anticipate marked alterations in the total phosphorus outgo directly related to changes in mental condition.

We have at hand, however, certain evidence which bears on this matter, and we submit the same, in brief, with the suggestions that such effects of mental disorder as have been observed on the phosphorus outgo are at least largely due to the indirect influence of the disease on general metabolism, *especially on muscular activity,* and on secretion and absorption in the alimentary tract, with the result of altered rates and paths of elimination; that in some cases the mental disorder may be the effect rather than the cause of a metabolic disturbance; and, further, that in the absence of feces analyses the urine data are of doubtful value in this relation.

NERVE DEGENERATION AND PHOSPHORUS METABOLISM

In the search for recognizable products of nerve tissue katabolism, which might serve as measures of this process, considerable attention has been bestowed upon choline, particularly in the cerebrospinal fluid, since Noll, Mott, Halliburton, Donath and others have demonstrated a slow autolytic liberation of lecithin and choline in degenerating nerve tissue. It has been suggested that choline, which is slightly toxic, and the highly poisonous neurine, which differs from choline by one molecule of water, may contribute to the production of the intoxication of fatigue, as well as acute mental and nervous disorders.

Coriat (1904a) found that choline was produced by autolysis of nerve tissue, and also by putrefactive decomposition of lecithin or tissues rich in lecithin, but not by cleavage by pepsin or trypsin.

Nesbitt (1899b) and Hoesslin (1906) have found choline and neurine as products of intestinal putrefaction, and Kutscher and Lohmann (1906) have demonstrated neurine in the urine of human beings.

According to Halliburton (1905) the existence of choline in normal cerebrospinal fluid, and in salt water extracts of fresh nervous tissue, implies chemical activity in living nerve substance, the more active part, the gray matter, yieldng the greater amount of choline.

Halliburton considers that the cerebrospinal fluid functions as the lymph of the brain, and that the increased choline content of the cerebrospinal fluid in *dementia paralytica* is directly due to decomposition of brain substance. In harmony with this idea is the finding by Donath (1904) of a coincident increase of phosphoric acid in cerebrospinal fluid in cases of degenerative lesion, the phosphoric acid also being considered as a product of lecithin decomposition.

PHOSPHORIC ACID (P_2O_5) CONTENT OF CEREBROSPINAL FLUID IN DISEASE (Donath, 1904) Grams

Cases	Diagnoses	Maximum	Minimum	Mean
2	Anaemia	0.0070	0.0064	0.0067
2	Neurasthenia	0.0278	0.0028	0.0153
7	Epilepsy	0.0209	0.0036	0.0086
3	Hysteria	0.0093	0.0065	0.0076
1	Pulmonary tuberculosis with melancholia	0.0026	0.0026	0.0026
2	Water on the brain	0.0116	0.0082	0.0100
2	Sclerosis multiplex	0.0051	0.0045	0.0048
2	Tumor on the brain	0.0286	0.0068	0.0177
6	Tabes dorsalis	0 0426	0.0046	0.0203
2	Progressive paralysis	0.0508	0.0052	0.0219

These figures show the highest phosphoric acid content of the cerebrospinal fluid in those diseases which are accompanied by rapid degeneration of nerve tissue.

For comparison with the above we have Mestrezat's average figure (1911) for the percent of P_2O_5 in 20 normal cerebrospinal fluids of 0.003.

Mott and Halliburton (1901) found choline in the cerebrospinal fluid and also sometimes in the blood in cases of severe nervous lesion, especially in paresis, and Donath (1903b) considers choline a factor in the causation of epileptic seizures, though he did not find choline in the cerebrospinal fluid in functional disorders not associated with tissue destruction. See also Masoin (1904).

Mott and Halliburton (1901) studied Wallerian degeneration, both chemically and microscopically. In a number of cats they severed both ischiadici. The animals were killed after different intervals of time had elapsed after this operation. The normal blood of the cat contains but the merest trace of choline, but in three or four days after the operation it became quite evident, at which time degeneration of the nerve was recognizable by Marchi's reaction. These symptoms were most pronounced in the nerve which had been severed for 8 days. Coincident with the increase of choline in the blood was an increase in the moisture content of the nerve and a decrease in the phosphorus content of the solid substance of the nerve. Regeneration was fairly complete after 100-106 days, the first sign of the return of phosphorus being the beginning of the response to the myelin reaction on the 60th day. In the normal nerve the phosphorus content is a little over 1 per-cent; in the regenerated nerve a little less than 1 percent. The moisture content returns to normal when regeneration begins.

These authors state that excessive degeneration of nerve tissue, either in general paralysis of the insane, or in other diseases, is accompanied by an accumulation of choline in the blood, and of loss of phosphorus in the nerve accompanying the change of lecithin to non-phosphorized fat.

Noll (1899) also conducted similar experiments with dogs and horses.

Mott and Barratt (1899) studied the chemistry of nerve degeneration by analysis of the spinal cord after hemiplegia. (See table, p. 539.) Their conclusions were as follows:

"On the degenerated side of the cord in simple hemiplegia it was found that (1) a breaking up of the phosphorized fat occurs; (2) the amount of lecithin present is diminished; (3) the amount of fat present is in excess; (4) the amount of extractives soluble in ether is increased; (5) the proteid residue diminishes in amount *pari passu* with the increase in extractives; (6) the phosphorus in the residue diminishes at a still greater rate than the residue itself; (7) the percentage of phosphorus in the half-cord as a whole is diminished; (8) the ether extract has an appearance of butter instead of being crystalline."

Coriat (1904b) has studied the cerebrospinal fluid in different nervous diseases, 29 cases being investigated. Choline was found in 25 and quantitatively determined in 21; was absent in alcoholic depressive hallucinosis, a senile paranoiac condition, melancholia and senile dementia. It was invariably present in general paralysis,

but no parallel could be observed between the amount of choline, the weight of the brain, and duration of the disease. The largest amounts of choline seemed to be associated with the highest percentages of protein, both being considered as measures of the extent of destruction of the central nervous system. Cholesterin was always absent. See also Apelt and Schumm (1908) and Coriat (1903), (34 cases discussed, 21 titles and references).

LECITHIN AND PHOSPHORUS DETERMINATIONS ON THE TWO HALVES OF SPINAL CORD AFTER LEFT HEMIPLEGIA

Mott and Barratt (1899)—Percent

Case	Lecithin		P in ether extract		P in residue		P in half-cord	
	Left side	Right side	Left side	Right side	Left side	Right side	Left side	Right side
I	18.9	22.2	1.72	2.14	0.92	0.97	1.19	1.38
II	20.7	23.5	1.84	1.93	1.03	0.98	1.38	1.42

Ziveri (1909) also found choline in the cerebrospinal fluid in paralysis.

Symmers (1904-5a, 1904-5b) reports that in nervous diseases of the degenerative type the absolute and relative amounts of organic phosphorus of the urine are increased, sometimes to an enormous extent, to such amounts as he considers could not be derived directly from the destruction of nervous tissues, but rather from increased production of phosphorized endogenous metabolic compounds, or as a result of lessened oxidation, with organic phosphorus compounds as end products.

W. Koch and W. H. Goodson (1906) published a preliminary study of nerve tissue degeneration. A normal human brain was compared with the brain of a paralytic, and a healthy spinal cord of a dog with a degenerated cord. (See numerical data p. 130.) They found a smaller content of solids in the degenerated brain than in the normal. Nucleoproteins were increased, according to the authors, by leucocytes, proliferating blood vessel elements and neuroglia cells. The cord of the dog, which was allowed to degenerate for 19 days after cutting, had a composition like that in the degeneration of general paralysis. The proportions of constituents remained unchanged, but the absolute amounts were reduced. The authors state in conclusion, "Nervous tissue more than any other tissue, both in pathological and in experimental degeneration, tends to keep its relative composition constant, which observation is in harmony with the results obtained in starvation."

W. Koch and Mann (1909) published analyses of brains of normal human beings and also of brains of four cases each of dementia praecox and general paralysis. (See p. 132.) The variations in the diseased brains were within the range of variation in the normal brains.

The present state of knowledge of the chemistry of the brain and of methods for its study do not begin to answer the requirements of such an investigation.

Pighini (1911) tested for esterase the blood serum in various nervous diseases such as epilepsy, idiocy from contusion of the brain, dementia praecox, alcoholism, etc., by the speed of reaction against neutral sodium monobutyrate, as shown by developing acidity; and compared these observations with others on normal serum. In most of these cases the action was slower than normal, although quite evident. Similar tests with a lecithin emulsion in sodium chloride solution showed the presence in all these cases of a lipase which would split lecithin, but only in the presence of a small amount of $MnSO_4$. It reached its maximum activity within the first hour.

The optical method (Pighini, 1910) was used for testing the serum for nuclease. In cases of alcoholism and epilepsy there seems to be less activity of the nuclease of the serum than is normal, during the interval between attacks; while in acute maniac depressive insanity, and in the period following epileptic attacks, this activity is increased.

Pighini and Nizzi (1912) report that neither in normal conditions nor in dementia praecox, epilepsy or progressive paralysis is there a specific esterase or lecithase in the cerebrospinal fluid.

PHOSPHORUS METABOLISM IN EPILEPSY

Lépine and Jacquin (1879) made a study of the proportions of phosphorus and nitrogen in the urine of 10 hospital patients and a number of dogs. In the case of certain epileptics, the relation of phosphorus to nitrogen is much lower than normal during the intervals between attacks. In the case of the same patients the relative amount rises remarkably immediately after the attack. Sometimes, without there being an attack, but only a threat of an attack, the relative amount rises, and this rise may be due to the alkaline earth phosphate.

Lailler(1884) reached similar conclusions, to the effect that at the time of the crisis or immediately thereafter, the urine contains an increased amount of phosphorus and a small amount of

urea, but when the crises succeed each other rapidly both phosphorus and urea are increased, while in the intervals between crises the urine is normal.

Mairet (1884c) investigated metabolism in various mental disorders. In epilepsy he found during attacks an increased urinary excretion of nitrogen and phosphorus.

Loewe (1910) also found an increased excretion of phosphorus in the urine of the day of the attack, both organic and inorganic phosphorus sharing in the increase, the latter, however, more than the former.

W. Koch (1904) published a brain analysis of an epileptic who had died in an attack. The analyses are submitted as provisional, and especially as illustrative of the methods of analysis.

COMPOSITION OF HUMAN BRAIN (EPILEPTIC)
Koch (1904) Percent

	Corpus Callosum		Cortex (Prefrontal)	
Water	67.97		84.15	
Simple proteids	3.20	(by difference)	5.00	(by difference)
Nucleoproteids	3.70		3.00	
Neurokeratin	2.70	(Chittenden)	0.40	(Chittenden)
Extractives	1.51		1.58	
Inorganic salts	0.82		0.87	
Lecithins	5.19		3.14	
Kephalin and myelin	3.49		0.74	
Amido lecithins	trace		trace	
Phrenosin and kerasin	4.57		1.55	
Cerebrin acids	trace		none	
Cholesterin	4.86		0.70	
Sulphur compound	1.40		1.45	
	99.41		102.58	

Loewe (1911) determined total and organic phosphorus in the urine of 33 subjects for 1-12 days after attack of various psychoses and neuroses. There was noted an increased organic phosphorus elimination after epileptic and some other attacks, and a probable increase in certain phases of paralysis and delirium tremens, though no increase in a number of other diseases in the psychiatric realm, as for instance in kakatonia. A. Bornstein (1911) found also a slight increase in the serum lecithin in epileptics. This increase of the lecithin content of the blood serum is regarded as indicative of increased katabolism of brain lipoids.

PHOSPHORUS METABOLISM IN PARALYSIS

Ewald (1883) determined phosphorus in the urine in 8 cases of paralysis agitans, chorea and senile tremor in periods of 2-33 days, also in four controls in periods of 12-23 days. The urinary phosphorus excretion was not in any way characteristic.

Gurther (1883), in somewhat extended studies, reached the same conclusion with cases of hystereoepilepsy and paralysis agitans.

Robert and Parisot (1906) studied 4 cases of paralysis agitans with trembling and one without. In the former cases they thought that the urinary phosphorus excretion was subnormal, but the basis for their conclusion is slight or of doubtful value.

Barratt (1899), studying the water and phosphorus in the central nervous system in general paralysis of the insane, and other conditions, found that there was a decrease in the phosphorus of the hemispheres of the brain associated with evidence of nerve-degeneration and of chromatolysis; and with increase in percent of water, but not proportional to any one of these conditions, or to the age of the patient, or the wasting of the hemispheres. A similar condition was found in the spinal cord.

Halliburton (1905) says that in general paralysis the cerebrospinal fluid is richer than normal in solids, especially in proteins, the most abundant of which being nucleoprotein; and much richer also in choline, both nucleoprotein and choline being considered as products of degeneration of nerve substance. See also Mott and Halliburton (1901) and Halliburton (1901b).

Glikin (1909a) estimated the lecithin of the marrow of the long bones of diseased persons. He found in five cases of *dementia paralytica* and in one of tabes (ages 33-43) no lecithin or only a trace, while in five others (ages 30-43) he found 1.195-4.21 percent. Where lecithin was absent phosphorus and iron were also absent. Glikin gives the following figures for the lecithin content of the fat of bone marrow of normal men.

Age 34	3.30 percent lecithin
Age 56	2.02 percent lecithin
Age 61	2.21 percent lecithin
Age 70	2.33 percent lecithin
Age 70	2.76 percent lecithin
Age 88	1.83 percent lecithin

A. Bornstein (1909) found an increased lecithin content of the blood serum in paralysis. Lecithin was determined by the Glikin chloroform method. He gives as the normal content of lecithin in blood serum 2.0-2.4 percent; in progressive paralysis he found 2.7-3.5 percent, and in taboparalysis 2.9 percent.

In a later publication (1911) Bornstein reports 11 cases of paralysis in which the lecithin content of the blood serum was determined. Two were considered as within the normal range of variation, these being 1.86 and 2.38 percent, while the remaining 9 cases ranged from 3.07-4.60 percent lecithin in the serum.

PHOSPHORUS METABOLISM IN INSANITY

Mairet (1884c), in studying phosphorus metabolism in mania, divided the observations into four periods covering different portions of the attack of the disease, as follows: agitation, depression, remission and convalescence. The results of this investigation are indicated by the accompanying table.

URINARY EXCRETION IN MANIA

Periods	Nitrogen	Phosphorus		
		Total	Alkaline earth	Alkali
Agitation	Increased	Increased	Increased	Increased
Depression	Diminished	"	"	Diminished
Remission	"	"	Diminished	"
Convalescence	"	"	"	"

In melancholia there was an increase in the alkaline earth phosphates, and a decrease of the alkali phosphates of the urine.

Lailler (1884) reached similar conclusions; that in acute delirium or mania there is a marked excess of urea and of phosphorus in the urine, in mania with excitement a slight excess of phosphorus only, while in simple mania, or in melancholia without agitation, the urine is normal. In acute melancholia, or with excitement, there is a notable increase in the urea and a slight increase in the phosphorus of the urine.

Modica and Audenino (1901) found in 10 cases of insanity, caused by immoral practices, a reduction in the alkali phosphates of the urine, and in certain cases also the total phosphorus. In 5 healthy guinea pigs and 2 healthy dogs, whose frontal lobes had been removed, the alkaline earth phosphates of the urine decreased, and finally disappeared, while the total phosphorus and the nitrogen also diminished.

Folin and Shaffer (1902) studied the metabolic accompaniments of a 48-hour periodicity of general nervous disturbance diagnosed as maniac depressive insanity. On the nervous days there was an increased amount of phosphorus, and an increased proportion of nitrogen and sulphur to phosphorus in the urine. The authors concluded, from the constancy of the percentage of alkali phosphates on four consecutive days, that the increase of phosphorus elimination on the nervous days was not due to katabolism of bone tissue.

As explaining the above phenomenon the authors suggest that "there exists in this patient on every second day a condition somewhat analogous to diabetes, in virtue of which the system, or some part of it, is unable to assimilate (organize) a part of the phosphate

absorbed from the digestive tract. The non-assimilated phosphate is eliminated on the same day, and the total amount of phosphate eliminated on the 'nervous' days is therefore greater than the amount eliminated by a normal person absorbing the same amount of phosphoric acid from the digestive tract. On the alternating days, on the contrary, a correspondingly less amount of phosphate than the normal is eliminated, because on those days the system repairs the loss sustained on the preceding days." The authors suggest further that it is the nervous tissues which are subject to the abnormal periodicity of ability to assimilate phosphates which produces the above described phenomenon. In view of the small amount (about 12 gm. P_2O_5) of the total phosphorus of the central nervous system, however, it is unlikely that the very considerable variations (about 0.66 gm. P_2O_5) in the daily urinary phosphorus excretion could depend directly on the state of nutrition of the nervous system. This investigation included no feces phosphorus estimations.

At a later date Folin, Shaffer and Hill (1904), after a careful study of the urines of insane patients and numerous controls, reached the following conclusions:

"From a constructive, positive point of view it must be admitted that they teach very little that is tangible concerning mental diseases, except for the strong suggestion which they contain that in general paralysis we have a disease which may be associated, at one stage or another, with some demonstrable metabolism disorder.

"From the destructive, negative or critical point of view, it is believed that the data given prove the untrustworthiness of all those metabolism experiments, old and new, which report a 'characteristic' increase or diminution of any of the urinary constituents included in this research as associated with any particular one of the ordinary mental disorders.

"It is not claimed that such abnormal metabolism may not exist, but simply that the experiments recorded in the literature are insufficient to demonstrate the fact."

Nizzi (1912) reports that the elimination of nitrogen and phosphorus is increased in the initial stage of maniac-depressive insanity and decreased in the chronic stage.

E. Mendel (1872) reported urine analyses from 110 patients suffering from various types of insanity and other nervous diseases, and of healthy persons; also the same from a dog and rabbit with the brain pierced by a needle. In the light of our present understanding, however, the results do not seem significant.

ADMINISTRATION OF PHOSPHORUS COMPOUNDS AND OTHER DRUGS IN MENTAL AND NERVOUS DISEASES

Pfeiffer and Scholz (1899) made a general metabolism and respiration study of senility and paralysis agitans as affected by thyreoidin.* Figures on phosphorus balance are as follows:

AVERAGE DAILY PHOSPHORUS BALANCES IN SENILITY AND IN PARALYSIS AGITANS AS AFFECTED BY THYREOIDIN—Grams

Exp. No. and duration in days	Condition and age of subject	Treatment	Intake P_2O_5	Urine P_2O_5	Feces P_2O_5	Balance P_2O_5
1a–6	Par. agitans, 57	Without thyreoidin	3.3155	2.3893	3.1798	–2.2374
1b–5	" " 57	With "	3.3593	2.8518	2.8703	–2.3628
2a–4	" " 57	Without "	3.9479	2.2340	3 4550	–1.7411
2b–3	" " 57	With "	4.3216	2.4538	3.4550	–1.5872
3a–4	" " 58	Without "	2.7716	2 0570	2.4057	–1.6911
3b–3	" " 58	With "	2.4491	2.2669	2.5385	–2.3563
5a–6	Healthy 76	Without "	2.0906	1.2095	3.7702	–2.8891
5b–5	" 76	With "	2.2473	1.8921	2.3958	–2.0406
6a–4	" 81	Without "	2.0906	1.3567	2.5346	–1.8007
6b–5	" 81	With "	2.2655	1.7317	2.4873	–1.9535

These results show both classes of subjects to be indifferent to thyreoidin, and that with paralysis agitans there is a marked increase of phosphorus outgo which, on the diet used, appeared in the urine. The authors regard this high phosphorus outgo as due more especially to senility than to paralysis agitans.

Gilbert (1901) reports general improvement in neurasthenics from the use of lecithin, either in pills, or in subcutaneous injections.

Kaufmann (1902) studied excessive protein ingestion in subacute neurasthenia, with a man 22 years old, on various simple diets, to which were added, in certain periods, the whites of 30-39 eggs per day. This excessive protein ingestion caused a reduction in the excretion of phosphorus by both urine and feces.

Martinet (1903) writes that phosphate therapy is beneficial both in accidental and in long-standing psychasthenia, but in psychatoxies with excitement phosphate therapy aggravates the pathological state. He bases his conclusions on clinical observations and examination of the urine after administration of officinal phosphoric acid, with sodium acid phosphate added to decrease the acid taste.

Donath (1903a) treated progressive paralysis, as well as toxic and infectious psychoses, 9 cases in all, by injection with a salt solution composed as follows: K_2SO_4 0.25 gm., KCl 1.0 gm., NaCl 6.75 gm., K_2CO_3 0.40 gm., $Na_2HPO_4+12H_2O$ 3.10 gm., and distilled water

* Thyreoidin is the same as thyroidin, an iodine-free, crystallizable compound from the thyroid; an amorphous iodine- and phosphorus-containing compound from this gland is known variously as thyrein, thyreiodin, thyroiodin, thyroiodinin and iodothyrin.

1000 gm. This solution was nearly isotonic with the blood. The treatment acted as a stimulus to the body functions generally, as indicated by improved heart action and appetite, increased diuresis, and particularly as a tonic to the nervous system as shown by improved handwriting, freshening of defective memory, increased accuracy of speech and singing, and ability to solve problems, etc.

Gordon (1906) reported clinical observations on 56 cases of nervous disease under treatment with phosphorus-containing drugs, with and without other drugs. Of the 56 cases 28 were multiple syphilitic affections of the nervous system, 5 were cases of tabes, 14 were neurasthenics, 2 melancholia, 3 cases of obcessions, and 4 of cerebral softening. Phosphorus-containing compounds had a beneficial effect on the asthenia, and apparently also improved the special symptoms of the disease itself. Glycerophosphates gave the best results.

J. Hoppe (1907b) has studied the effects of adding thyroid tablets to the food in treatment of three kinds of idiocy, namely myxoedema, cretinism, and "mongoloid" idiocy. In myxoedema there was a marked increase in the apparent absorption of calcium and phosphorus, and a noticeable growth of the bones. In cretinism there was but slight improvement in the absorption of calcium and phosphorus; and in mongoloid idiocy none at all. As a result of a vegetable diet and rectal feeding with 5 gm. Na_2HPO_4 daily, the patient with myxoedema showed improved calcium absorption and a simultaneous increase in the phosphorus outgo in the urine. See also Tuczek (1884).

Peritz (1908, 1908-9a) found an apparent increase of lecithin in the feces in lues, tabes and paralysis; and also that lecithin injection would reduce the increased lecithin elimination in these diseases. A large number of estimations of the lecithin in the blood serum in the above-mentioned, and in other diseases, were presented (1908-9b). The results were characterized by much variability. Lack of normal controls leaves uncertain the significance of these observations by Peritz. In a later paper Peritz (1910) shows that the lecithin of the blood serum responds readily, by marked increase, when lecithin is administered *per os*

Taghamuro (1908) administered lecithin by injection in dorsal tabes. There resulted improvement of digestion, appetite and general condition, as well as increase of red blood corpuscles and haemoglobin.

Nerking (1909) made an extensive study of the effects of lecithin on narcosis. With considerable numbers of rats, dogs and rabbits, with the usual use of controls, he treated them with anaes-

thetics as follows: ether, chloroform, morphine, scopolamin, urethan, urethan-chlorhydrate, novokain-suprarenin, tropakain and stovain, usually as subcutaneous, intraperitoneal or intralumbar injections, and followed these treatments with injections of 1-10 percent solutions of purified lecithin. In all cases the lecithin injection is said to have produced a favorable effect on narcosis (1) in shortening the period, (2) in the alleviation of unfavorable after-effects and (3) in causing a rapid return to normal condition.

Donath (1909) experimented with 2-percent sodium nucleate, containing an equal quantity of sodium chloride, by subcutaneous injection in 21 cases of general paralysis, in amounts of 50-100 c.c. at intervals of 5-7 days. The injections caused a rise of temperature, in some cases to 40.5° (average 38.5°), and an increase of leucocytes to 61000 (mean 23000). Out of 21 cases 10 were sufficiently improved to return to ordinary duties (the oldest case was of two years' standing); in 5 cases there was improvement, while 6 remained unimproved.

Klieneberger (1911) and Löwenstein (1911) report negative or unfavorable results from the use of sodium nucleinate, by injection, in progressive paralysis.

For the successful use of a lecithin preparation in migraine see Schottin (1911).

Leubuscher (1913) gave elemental phosphorus in 10000 parts of oil in 9 severe old cases of epilepsy. Seizures were reduced by 30 or 40 percent in 3 cases, about 65 percent in two others; in 3 others the improvement was less striking, while with one patient there was no improvement. The greatest benefit was obtained in the more severe cases. Phosphorus was administered for 15 months with 6 cases.

NEPHRITIS

Fleischer (1881) found in chronic interstitial nephritis a decreased excretion of phosphorus, and a parallelism between nitrogen and phosphorus elimination by the kidneys. Sodium phosphate ingestion led to quantitative excretion of the phosphorus within 24-48 hours in a normal subject, but in nephritis produced little or no increased phosphorus excretion—a difference not noted with respect to potassium bromide and sodium salicylate. In a case of lighter acute nephritis there was a marked lowering of urea and phosphorus in the urine.

VanAckeren (1890-91) and Kornblum (1892) found neither a parallelism of urea and phosphorus elimination nor a consistent lowering of phosphorus elimination.

Von Moraczewski (1896) showed that in parenchymatous nephritis the urine contains less chlorine and more phosphorus, especially calcium and magnesium phosphate, than normal. In interstitial nephritis, however, there was no increase of urinary phosphorus; in fact a decrease of calcium and magnesium phosphates. Uric acid was found increased in parenchymatous nephritis and normal in the interstitial variety.

Mohr (1903) published food and urine analyses from four nephritic patients. The data show plainly that the phosphorus outgo is normally affected by variations in the intake.

Von Koziczkowsky (1903-04) found in nephritis that the outgo of phosphorus varied normally with the intake, and that the phosphorus outgo was indirectly proportional to the sodium chloride retention.

Kövesi and Róth-Schulz (1904) found in nephritis that the proportion of the total phosphorus of the food, which appeared in the feces, varied widely without ascertainable relation to food or pathological conditions. In their cases they found almost constant phosphorus retention, reaching very high figures in cases of rapidly developing oedema; but they noted no relation between phosphorus elimination and the form or symptoms of the disease, or the nitrogen or sodium chloride of the urine, or the total of dissolved molecules in the same. These authors consider it desirable to restrict the absorption of phosphates in nephritis, and they note von Noorden's suggestion that calcium carbonate be given with the usual milk diet in the accomplishment of this purpose.

Von Noorden (1907, II, p. 467) mentions a number of investigations, in addition to those which we have seen, in which the capacity of the kidneys to eliminate phosphorus was not lowered, and also several investigations showing that the observation of von Koziczkowsky of the reciprocal relation of phosphates to sodium chloride was not the rule; hence, we are unable to say that there is any invariable character of the urinary phosphorus elimination in nephritis, though a retention of phosphorus, apparently an expression of a lowered capacity of excretion, is very common. The significance of this variation is not known.

Erben (1903, 1905) found low values for phosphorus in the blood in subchronic nephritis, in chronic parenchymatous nephritis, and also in cases of secondary shrunken kidneys.

J. Müller and H. Reinbach (1913) studied digestive lipaemia in a case of subacute nephritis. Lecithin was present in the serum to the extent of 0.688 percent.

NUCLEIN THERAPY

This subject is discussed in connection with normal nuclein metabolism; see p. 256-258.

OEDEMA

L. E. Meyer (1905) studied the effect of variations in the water, sodium chloride and phosphorus content of the food of a nursing infant suffering from idiopathic oedema. The addition of 200 c.c. of distilled water per day to the food was without marked influence on mineral metabolism. Where sodium chloride was fed in varying quantities the storage varied directly with the intake; and where sodium phosphate was added, the sodium chloride intake remaining constant, there was marked increase in the storage of both phosphorus and sodium chloride, and a decrease to more nearly the earlier retention figures when the phosphate was withdrawn. Meyer was of the opinion that the above-mentioned storage was pathological in character, in that the outgo was not normally responsive to the intake; that the cause was a functional disturbance of the epithelial cells of the uriniferous tubules, resulting in an overloading of the blood with salts, and therefore in oedema; and further, that the treatment for idiopathic oedema should be the decrease of the salt content of the food to the lowest possible amount.

EFFECTS OF MISCELLANEOUS ORGANIC PHOSPHORUS-CONTAINING COMPOUNDS AND PREPARATIONS ON PHOSPHORUS METABOLISM

TETRA-ETHYL-PHOSPHONIUM IODIDE

Lindemann (1898) studied the pharmacology of tetra-ethyl-phosphonium iodide by injection experiments with frogs, rabbits, guinea pigs and dogs. The action of this substance is characterized by loss of coördination, and general paralysis, which soon extends to the respiratory center and then to the heart, which is invariably found engorged and in diastole. The lungs are strongly hyperaemic and oedematous, while in chronic intoxication there are characteristic changes in the liver and kidneys, consisting in hydropic, albuminotic degeneration of the protoplasm. A full statement of details is given. This substance is excreted in the urine together with a compound giving an insoluble precipitate with barium, and a volatile base, which, with sulphuric acid, forms a non-volatile salt. The only marked pathological change in the urine was a decided haemoglobinuria, appearing in the last stages of chronic intoxication. It is therefore shown that neither the lower oxidative stages of phosphorus, nor phosphine, nor the organic phosphorus compounds have the action of elemental phosphorus.

FERSAN

Kornauth and Czadek (1900) experimented with fersan, a beef-blood preparation containing much iron and phosphorus in a mixture of organic combinations. With this preparation two experiments were conducted, one on geese and another on a man.

Two geese were fed 240 gm. corn each per day. In addition one received pellets of fersan. In two 7-day periods the one receiving corn alone gained 70 and 230 gm. in live weight, while the one receiving the fersan with its corn gained 195 and 235 gm. during the same periods.

In four balance experiments of 6-15 days duration with a man, two periods with fersan and two without, there was no evidence that this preparation could improve a mixed diet containing an abundance of meat, though the authors state that it was almost completely absorbed and assimilated.

ROBORAT

Laves (1900) studied the nutritive value of prepared proteins, roborat (prepared from grain; contains lecithin), tropon (from flesh and blood), aleuronate (from wheat), and plasmon (from milk). Experiments of short duration were conducted on the author and on a dog, with artificial digestion tests. Urine analyses furnished the basis for conclusions. The results are not significant.

CARBOHYDRATE-PHOSPHORIC ACID ESTERS

Euler (1912b) investigated the disposition by animals of the carbohydrate-phosphoric acid ester synthesized by yeast. His conclusions are in part as follows:

This ester is split by an intestinal enzyme and by *Bacterium coli;* also by an enzyme contained in the kidney of the horse. The calcium salt of this ester is broken down and the inorganic phosphate excreted as such. The calcium salt of glycerophosphoric acid ester is likewise broken down by *Bacterium coli.* The calcium salt of the phosphoric acid ester when fed to dogs goes over largely into the urine as inorganic phosphate.

From a study of the literature Euler concludes that organic phosphorus in the food is absorbed both split and unsplit. He suggests that "it is especially to be emphasized that the physiological effects of phosphates are to be sought in their remarkably strong influence on the vital enzyme reactions."

Euler and Funke (1912) report an experiment with the carbohydrate-phosphoric acid ester formed by phosphatese, the compound being fed to a rabbit. At least three-fourths of the ester underwent cleavage.

For discussions of nuclein, lecithin and phytin therapy see pages 256, 528 and 315 respectively.

PROTYLIN

Protylin is a phosphorus-containing preparation obtained by the dialysis of egg-albumin after protracted treatment with orthophosphoric acid. It is a white, tasteless powder, insoluble in water, and contains 2.7 percent of phosphorus.

Gnezda (1903) reported clinical observations on 11 cases of cachexia with carcinoma, hysteria, anaemia, nervous dyspepsia, etc., under treatment with protylin, which is said to have proven itself a valuable tonic, as evidenced by increase of appetite, body weight and haemoglobin, and improved psychic conditions.

Siegmann (1904) published similar observations on 32 cases, as also did Marian von Bilgorajski (1904) on 10 cases, the latter recommending especially the iron and bromine compounds. See also Dorn (1904). Laumonier (1905) submits other clinical data.

Pouchet and Chevalier (1905) conducted injection experiments with a protylin solution, 38 gm. protylin and 2 gm. soda per liter of water, with dogs. After injection for 2 hrs. 35 minutes into a chloralized dog a sharp decrease in blood pressure occurred, and an accelerated and subsequently retarded cardiac action. Afterward the blood pressure slowly became normal, if the injections were continued more feebly, the cardiac action being accelerated simultaneously.

In the case of a dog with section of the pneumogastric nerves there took place a more marked acceleration of cardiac action, the blood pressure decreased less; on the other hand a lessening of the cardiac energy followed, which caused the heart to fail to become completely filled. These authors consider that the action of this phosphorus preparation on the circulation accounts to a great extent for its influence on the general nutrition.

Timpano (1906) reports increase of appetite and of strength, reviving of psychic activity, and improvement of general state of nutrition from the feeding of protylin to 18 cases, and Gallenga (1906) made similar observations on 22 cases.

R. O. Neumann (1906) showed that protylin, when used in varying amounts to replace equivalent amounts of cheese protein in a mixed ration, does not increase either nitrogen or phosphorus retention. When added to a full diet, however, its nutritive value was apparent, and both nitrogen and phosphorus storage were increased.

Fjodoroff (1907) determined that the ingestion of lecithin, nucleic acid and phytin often causes a slight increase of free hydrochloric acid in the stomach, sufficient in cases of chronic

hyperacidity to cause heart-burn, and to constitute a contraindication of their use. In such cases protylin, even in 5-gram doses, is well tolerated.

See also Maëstro (1905a), Wechsler (1905) and Laguesse (1905).

OSTEOMALACIA

Osteomalacia in human beings is a disease of entirely unknown cause, one of the prominent symptoms of which is an absorption of the salts of bone, and their replacement by tissues not having the normal content of bone salts. It is not due primarily to lack of phosphorus or calcium compounds in the food, nor to rapid growth, or pregnancy, or lactation, or senility, though naturally these may all be contributory or accentuating conditions; and it is not curable by the use of foods which are rich in bone-forming constituents.

The literature of this disease is very voluminous, and of it we have seen but a small part. There is little variety in the experimental findings, and our materials are perhaps typical of the whole body of facts as published.

LACTIC ACID IN OSTEOMALACIA

An early idea regarding human osteomalacia was that the bone salts were removed by an excess of acids in the system, and lactic acid seems occasionally, though not as a rule, to have been found in the blood, urine and bones.

C. Schmidt (1847) reported a case of bone disease involving all of the bones of one leg, resulting in the absorption of nearly the whole of the mineral substance, the periosteum remaining intact. Analysis showed the soft inner portion of the bone to contain much lactic acid; but Virchow (1852) discusses a fatal case of puerperal osteomalacia in which the bones had become filled with a soft jelly-like substance of alkaline reaction.

O. Weber (1867) found lactic acid in osteomalacic bones, and Steiner (1869) made an anatomical study of senile osteomalacic bones, and concluded that the disease was due to removal of the lime salts by lactic acid.

Note: Osteomalacia of the domestic animals, which is also known as **malnutrition of** the bones, halisteresis of the bones, fragility of the bones, and osseous cachexia, differs from human osteomalacia. This malady is without doubt due principally to deficiency of the food in bone-forming constituents, though perhaps also in part to a lack of correct proportion between the mineral elements, bone-forming or otherwise, contained in the food. This condition is readily curable, simply by the removal of the cause, though in the course of time affected animals may become more or less unresponsive to improved conditions of diet. The principal predisposing conditions are pregnancy, lactation, growth, starvation, and unhygienic surroundings. The use of the term osteomalacia for this simple malnutrition of the bones is confusing and should be abandoned.

Mörs and Muck (1869) found much lactic acid in the urine of one case of osteomalacia, a little in the urine of another, and none in the urine of a third case. They consider excessive production of acid to be the cause of osteomalacia. In one case, which was cured by the use of a nourishing diet, cod-liver oil, and a salt mixture of calcium carbonate, calcium phosphate and ferric hydrate, the lactic acid disappeared from the urine as the bones began to harden.

See also von Jaksch; Ueber die Alkalescenz des Blutes; Zeitschr. f. klin. Med., 13, 355.

Heitzmann (1873) administered lactic acid subcutaneously, and with the food, to 7 cats, 5 dogs, 2 rabbits and 1 squirrel, the food being low in lime; and the experiments were continued for several months, in one case at least, 13 months, followed by examination of the bones.

After two weeks' administration, by either method, the carnivora showed rachitic symptoms, swelling of the epiphyses of the long bones and of the union of the costal cartilage with the ribs. The swellings mentioned increased visibly by the 4th and 5th weeks; the long bones became crooked, and the microscopic examination of the epiphyses agreed perfectly with that of rachitic children.

After 4 to 5 months' feeding of the acid the long bones became as flexible as fish bones. The microscopic structure of the bones after 4 to 11 months' feeding of lactic acid was analogous to that of people who had died from osteomalacia.

With the three herbivora the case was different. The walls of the long bones of the rabbits became very thin, but remained brittle; while with the squirrel, which was fed for 13 months, the walls of the bones became very thin and also flexible.

Unfortunately in these experiments there were present two possible demineralizing agencies, and it is impossible to say whether the results were due to calcium starvation alone, or in part to the effects of the acid.

Vogt (1875) injected into the tibiae of living rabbits, five weeks old, 2 drops of pure lactic acid. The rabbits were killed 5 months afterward. The periosteum was rather easily separable from the rough surface of the bones, and there appeared to have been hyperplasia of the bone tissue, the bones having increased to nearly 3 times the size of the uninjected tibiae. Parallel punctures without acid produced no such result.

All things considered, however, these facts probably no longer have significance.

Rudolph Wegner (1876) reports that 1:3 or 1:5 lactic acid solution injected under the periosteum causes solution of the bony substance, 1:10 acid showing no such effect.

Heiss (1876) investigated the question as to effect of lactic acid ingestion on the composition of the bones of a dog. The feeding of lactic acid covered 308 days. The body of the dog was then analyzed. The acid was administered at first in quantities of 1-2 gm. daily, but during the greater part of the test in quantities of 7-9 gm. daily. The author discovered no solution of the mineral constituents of the bone by the lactic acid.

Langendorff and Mommsen (1877) reported a study of a fatal case of osteomalacia in a man 35 years old. Lactic acid was not found in the bones.

Baginsky (1881) fed 3 young dogs, all from the same litter, on a ration which was nearly free from lime. To this diet was added, with one dog, 2 gm. lactic acid per day, with another 2 gm. calcium phosphate, and the third received the basal ration alone. The calcium starvation caused by the basal ration led to a reduction of the ash of the bones, and with the dog receiving lactic acid this effect was said to be still further emphasized.

Hofmann (1897) cites cases of osteomalacia in which no lactic acid was present in the urine.

Klotz (Jahrb. f. Kinderheilk., **70**, 1-61) found that large doses of lactic acid disturb fat and mineral metabolism. The disturbance of the fat metabolism may have been due to the neutralization of the alkali carbonates by the acid, with the consequent formation of insoluble calcium and magnesium soaps. The phosphoric acid, no longer combined with the calcium as insoluble phosphate, could combine with the alkalis to form soluble compounds, thus increasing the absorption of phosphorus.

Siedamgrotsky and Hofmeister (1879) published results of experiments with sheep and goats which received in addition to a ration of normal foods and pasture grass either lactic, sulphuric or hydrochloric acid. The results are in the nature of analyses of the bones, balance experiments and analyses of the milk. In our opinion the results are inconclusive.

Moritz Levy (1894) finds that lactic acid removes carbonate more rapidly from normal bone than it does phosphate, and that therefore there is no solution of bone salts by an acid in osteomalacia. This view of the matter prevails at this time.

Bonnamour and Escallon (1913) studied, with a rabbit, the effects on the bones, of intravenous injection of lactose. During 3 months one rabbit received 378 gm. of lactose in this manner in doses of 10 gm. each. Analysis of the bones revealed the following:

COMPOSITION OF BONES AS AFFECTED BY LACTOSE INJECTION
Pecent of Dry Bones

	Control	Treated
CaO	31.66	24.8
MgO	0.60	3.04
P_2O_5	16.63	25.5

These data imply a decalcification and an increase of magnesium and phosphorus.

COMPOSITION OF THE BONES IN OSTEOMALACIA

A considerable number of analyses of osteomalacic bones have been published. One of the earlier studies is that of Mörs and Muck (1869). Their figures show considerable variation in the proportions of the different mineral constituents, with a marked loss of mineral matter generally, and of calcium, a less marked loss of phosphorus, and an increase in magnesium. See also von Gohren (1865), Huppert (1867) and Regnard (1879).

The method by which these changes are produced, as stated by Pommer (1885), is through a continuous building of new lime-free bone tissue, a cessation of the deposition of lime, and a local removal of lime from parts containing it. See also von Recklinghausen (1891).

Moritz Levy (1894) submits extensive figures on the composition of osteomalacic bones, and numerous citations of the work of others. He concludes that the relation 6 PO_4:10 Ca, of normal bones, remains the same during osteomalacia, and that the removal of phosphate takes place in the same quantitative relation as that of the carbonate. Levy's own figures, however, show changes in the proportion of phosphorus to calcium of various degrees up to one-twelfth of the total.

Galimard and König (1905) publish analyses of bones from a case of infantile osteomalacia which show a marked change from the normal relation of calcium, magnesium and phosphorus. The following figures are from this article.

PERCENTAGE COMPOSITION OF NORMAL AND OSTEOMALACIC BONES—Fat- and Water-free Basis

	Normal Femur	Osteomalacic Femur
Ossein	33.35	55.03
Phosphate of lime	55.84	38.07
Carbonate of lime	6.33	6.38
Phosphate of magnesia	0.79	0.49

McCrudden (1906a) found in the osteomalacia of horses, in harmony with the conclusions of Roloff (Virchow's Archiv, 37, 433), Huppert (Archiv der Heilkunde, 1866, 1867, 8, 345) and

Chabrié (Les phénomène chimiqué de l'ossification, Paris, 1895, p. 65), that there was a decrease of calcium and phosphorus, and an increase in magnesium and sulphur. The following data are from this article.

PERCENTAGE COMPOSITION OF RIBS OF HORSE, NORMAL AND OSTEOMALACIC

	Osteomalacic		Normal	
	I	II	I	II
CaO	20.09	18.35	33.48	33.12
MgO	0.50	0.46	0.11	0.10
P_2O_5	16.55	16.00	23.66	23.22
S	0.35	0.38	0.11	0.09

Cappezzuoli (1909b) publishes analyses of long bones and flat bones from a case of osteomalacia. He found a general demineralization of the bone, but a greater proportionate loss of calcium than magnesium. In the long bones he found Ca:Mg: :100:2.66 and in the flat bones Ca:Mg: :100:3.85, while in the normal the ratio of Ca to Mg is as 100:1.14.

McCrudden (1910b) published a chemical analysis of bone from a case of human osteomalacia. The results are as follows:

	Osteomalacia Percent	Normal Percent
CaO	15.44	28.85
MgO	0.57	0.14
P_2O_5	12.01	19.55
S	0.55	0.14

These figures show a great decrease of calcium, a less marked decrease of phosphorus, and four-fold increase of both magnesium and sulphur. While the cause of the deposition of the salts in bone is not definitely known we must admit (1) that there resides in the osteogenous tissue some property which acts like an affinity for the bone salts, (2) that this affinity tends to maintain a constant proportion between the salts deposited, but (3) that variations in the composition and reaction of the blood, as affected by disease, modify the character of this affinity, as indicated by the composition of the bones, in definite and consistent ways, even if not to unlimited degrees.

METABOLISM IN OSTEOMALACIA

Mohr, in von Noorden's "Metabolism and Practical Medicine," tabulates calcium, magnesium and phosphorus balances by von Limbeck (1894), S. Neumann (1894a, 1894b) von Korczyński (1902),

Sauerbruch (1902), Goldthwait *et al.* (1905), and Hotz (1906). Improved physical condition of the patients was usually accompanied by increased retention of the bone salts. Phosphorus retention was commonly disproportionately large, as compared with calcium, and both may be retained in moderately severe cases.

Von Korczyński (1902) reports balance data with two cases of osteomalacia showing that if the disease is not too far advanced, and the course of the disease not rapid, and no marked cachexy is apparent, the organism retains phosphoric acid.

Earlier metabolism studies showed considerable losses of calcium, magnesium and phosphorus, not only in the urine but also in the feces, in bronchial mucous in cases associated with bronchial catarrh, and also in the milk. See Pagenstecher (1862), Gusserow (1862), Schmuziger (1875) and von Limbeck (1894).

Raspopoff (1884) finds the proportion of the urinary phosphorus united to alkaline earths greater, and that united to the fixed alkalis less, in osteomalacia than the normal. See also Raspopoff (1885).

Metabolism studies by S. Neumann (1894a, 1894b) show that a predominating loss of phosphorus may change to as considerable a retention of the same as the case improves, while on the other hand the work of His (1902), on a case of infantile osteomalacia, shows that improvement may be due to improved retention of calcium, the preëxisting positive phosphorus balance remaining without striking change.

The existence of typical osteomalacia in children was attested by investigations of Siegert (1898), who cites a previous demonstration by von Recklinghausen, and also by the above-mentioned work of His.

Very few studies of the blood in osteomalacia have come to our attention. Fehling (1891) reports subnormal alkalinity in the blood in severe cases; Pende (1905) found improved blood conditions as determined by corpuscle count, etc., after phosphorus therapy. Kobler (1888) also publishes blood ash analyses contrasted with the normal, with results as follows:

COMPOSITION OF ASH OF BLOOD

	Osteomalacia	Normal (Jarisch, mean of four)
Phosphoric anhydride	7.2	8.49
Sulphuric anhydride	16.04	6.85
Chlorine	19.925	29.59
Potash	34.160	25.565
Soda	9.35	23.169
Lime	0.52	0.872
Magnesia	...	0.512
Iron oxide	12.85	7.86

A somewhat recent idea as to the cause of osteomalacia is that of Hoennicke (1904, 1905) (10 pp. bibliog.), who considers it due to disease of the thyroid gland.

Zunz (1913) found in osteomalacia no characteristic variation in protein metabolism. The phosphorus metabolism was quite variable, but a high fecal outgo was rather constant, this elimination being usually reduced by ovariotomy, with increased tendency to retention.

TREATMENT OF OSTEOMALACIA

In the treatment of osteomalacia His (1902) notes favorable results from the use of phosphorus, first by Trousseau in 1868, later by Wegner in 1872, cites Sternberg's report (1893) of eight cured cases from the clinics of Busch, Strümpell, Matterstock and Nothnagel, and also his own description of four other such cases, also favorable results by von Limbeck (1894), Kosminski (1896), Bernstein (1898), Heubner (1898), Siegert (1898) and Littauer (1899). He also cites unfavorable reports of the use of phosphorus in osteomalacia by Gelpke (1891), and Fehling and Wetzel (1899).

Other favorable reports from the use of phosphorus in osteomalacia have been published by Warschauer (1890), Sternberg (1893), H. Fischer (1894), Pende (1905) and Hotz (1906).

Treatment with oöphorin and thyraden by Senator (1897) led to improvement in the patient, but treatment with oöphorin by Bernstein (1898) failed, after which phosphorus therapy caused a cure.

Ovariotomy has given good results in a number of cases but there is no established connection between the ovaries and osteomalacia. Beneficial results seem to be due especially to the prevention of loss of calcium and phosphorus from the body through the various incidents of the sexual life.

Fehling (1891) reports cases of ovariotomy, and later (1895) 10 cures from 12 such operations. Curàtulo and Tarulli (1895) also report favorable results from ovariotomy.

S. Neumann (1896) reported metabolism data with cases of ovariotomy in osteomalacia. This treatment is regarded as radical, and not generally to be recommended, though benefit resulted in case the disease was not too severe. Results were unfavorable in advanced cases.

Goldthwait, Painter, Osgood and McCrudden (1905) made balance experiments on a 16-year-old osteomalacic, both before and after ovariotomy. Before the operation there was a marked loss

of calcium, a slight loss of phosphorus, and a slight storage of magnesium. Some months after the operation the patient was found to be storing calcium, but magnesium and phosphorus determinations were not made. These authors consider that their balances indicate a partial replacement of calcium by magnesium previous to the operation.

McCrudden (1906b) reports a later metabolism study on the same case of osteomalacia that was studied a year and a half before by Goldthwait *et al.*, and found much improved by ovariotomy. At the time of this later study the patient was once more in a critical condition, and was found to be losing calcium and magnesium, but retaining phosphorus. As to the connection of the ovaries with osteomalacia it was McCrudden's idea that ovariotomy is without influence on the ultimate cause of the disease.

In accord with this idea we have the results of Lüthje (1903), who showed by the removal of testes and ovaries from dogs that neither organs bear any noticeable relation to phosphorus metabolism generally.

Curshmann (1911) describes cases of osteomalacia in men and women of middle age and old age. Cure was effected by the use of phosphorized cod-liver oil.

In this connection we have also considered the paper of Ogata (1911-12).

PHOSPHORUS METABOLISM AND THE PARATHYROIDS

The extirpation of the parathyroids reveals an essential relation of these glands to metabolism, the nature of which is as yet but imperfectly understood. The following notes show that they are intimately connected with phosphorus metabolism.

Morel (1910) notes that parathyroidectomized animals fail to heal fractures as rapidly as normal animals, the conversion of cartilage to bone being slower. Removal of the thyroid was without appreciable effect on the bones. Also (1909) administration of thyroid substance was without effect on the bones of adult animals, while the feeding of parathyroid extract to young rabbits favored the growth of the bones independently of the calcium of the ration.

Erdheim (1911) found that in rats, after parathyroidectomy, the new bone produced is very poor in calcium, and that the skeleton generally takes on an osteomalacic or rachitic character.

T. Bauer (1911) supports Erdheim's findings of parathyroid hyperplasia in human osteomalacia, which hyperplasia is ascribed to an increased functional demand for calcium.

Erdheim also finds that after parathyroidectomy the dentine calcifies late, or not at all; that the enamel is deficient, and that fractures of the bones are frequent, but that if parathyroids be successfully transplanted into these parathyroidectomized animals the dentine calcifies; if they are then removed the dentine forms without calcium.

Toyofuku (1911) made a histological study showing that deficient deposition of calcium is responsible for the structural change observed.

These above observations regarding calcium involve, of course, phosphorus, without which calcium could not be used in the normal growth of bone.

Greenwald (1911, 1913a) found that parathyroidectomy caused a very marked phosphorus retention, which was followed, but not until the appearance of tetany, by an increased excretion of phosphorus. In another paper (1913b) Greenwald reported that after parathyroidectomy the phosphorus of the blood is increased, the greater part of this increase being in the fraction which is insoluble in the usual lipoid solvents, but is soluble in a mixture of dilute hydrochloric or acetic and picric acids. Some of Greenwald's data are as follows:

PHOSPHORUS IN BLOOD FROM A THYRO-PARATHYROIDECTOMIZED DOG AND A NORMAL DOG—Milligrams of Phosphorus per Kilo of Blood

Phosphorus	Parathyroidectomized 214	Normal 214B
Total	436	370
Extracted with acetone	162	140
Extracted with alcohol and ether	8	7
Extracted with picric-hydrochloric acid	233	192
Not accounted for (protein phosphorus?)	33	31

PHOSPHORUS IN SERUM FROM PARATHYROIDECTOMIZED AND NORMAL DOGS—Milligrams of Phosphorus per Kilo of Serum

Phosphorus	Parathyroidectomized			Normal		
	Dog 215	Dog 217	Dog 219*	Dog 216	Dog 218	Dog 220
Total	212	222	291	157	244	167
In acetone extract.	149	128	194	131	186	110
In acid extract	62.3	76.7	87.7	26.9	44.4	45.5
Residue			3.8		2.4	

* Complete thyroidectomy in this case.

Paladino (1913) considers that after the removal of the thyroid and parathyroid glands urinary phosphorus elimination increases greatly, but Greenwald (1913c) states that the removal of these organs reduces phosphorus elimination, and that there is no increase until the appearance of tetany, the increase then being due to the muscular activity.

PHOSPHATURIA

Phosphaturia is not a disease; it is a symptom or condition which may result from many causes, normal as well as pathological. It is said to exist when, from whatever cause, there is a sediment of alkaline earth phosphates, which may be mixed with carbonates, in the fresh urine. The immediate cause of the sediment is a relative increase of alkalis or alkaline earths, or a relative decrease of acid elements. In either case the increase or decrease may be relative without being absolute; hence the existence of the phosphate sediment is no indication of the amount of phosphorus in the urine. It may occur with increased or decreased phosphorus so long as there is sufficient relative increase of alkali or alkaline earth.

The method of formation of the sediment is a change, under the influence of alkalis or alkaline earths, of a portion of the soluble diacid-phosphates normally present into the insoluble monacid or normal phosphates.

This condition may result from any such change of diet as increases to a sufficient extent the carbonates or oxidizable organic compounds containing alkalis or alkaline earths; or through any such influence as decreases the acids normally excreted in the urine, such circumstances for instance as the ingestion of much protein, or continued washing out of the stomach, both of which result in the separation from the blood of unusual amounts of hydrochloric acid, and liberate within the blood corresponding amounts of alkali.

Another form of phosphaturia, common in children, is due to a deflection of calcium from feces to urine without necessary change in the amount of either calcium or phosphorus, the cause not being established beyond possibility of doubt, but commonly thought to be such pathological condition of the large intestine as results in decreased ability to excrete calcium.

Aside from matters of diet and digestive disorder it seems likely that nervous influences affect metabolism in such ways as to cause phosphaturia, either combined or not with the juvenile form above described; and phosphaturia is common in many diseases; for instance, in some cases of diabetes mellitus, in tuberculosis, and in such bone diseases as ostitis and osteomyelitis.

It is impossible for us to attempt a review of the enormous literature of this subject, but we shall record observations on a few of the more important articles which have come to our attention.

One of the more important of the earlier works on phosphaturia is that of Teissier (1875, 1877). He found that it was a condition not particularly connected with alterations in skeleton or nerves. A part of his conclusions are as follows:

"Permanent phosphaturia always indicates serious trouble in the general nutrition. The trouble may be profound enough to show all the apparent symptoms of sugar diabetes. But phosphaturia of the diabetic form is not an essential disease, but is rather a morbid complication which may be sympathetic of various affections. It may be a simple form of nervousness which accompanies pulmonary phthisis, or may be a precursory sign of it. It may be symptomatic of sugar diabetes, latent or transformed. Diabetic phosphaturia may, like sugar diabetes, exert an evil influence on the progress of traumatic lesions."

"Phosphates are abundant in the urine of consumptives at the beginning of the disease; they diminish somewhat as the period of tuberculous cachexy arrives. They diminish in true chlorosis. They increase in diseases of the brain, and of the marrow. They increase in chronic rheumatism. They decrease generally in the course of fever and ague. They do not increase in spite of most abundant feeding in the course of convalescence; rather they are diminished."

Ralfe (1887) classified cases of phosphaturia coming to his attention (1) as associated with disturbances of the nervous system, (2) as associated with pulmonary disease, (3) as alternating or coexisting with saccharine diabetes and (4), as without special connection.

Sendtner (1888) showed in a single case that excess of lime was the cause of phosphaturia.

Peyer (1889) also considered excess alkalinity of the blood as the cause of phosphaturia.

Klemperer (1899) considered phosphaturia as due to hyperacidity and motor insufficiency of the stomach, the former taking abnormal amounts of acid from the blood, and the latter by retaining it over-long in the stomach, delaying its return in compensating amount by way of intestinal absorption. Klemperer considered both of these symptoms as due to nervous affection.

Leo (1902) reported a case of phosphaturia in which there was abundant phosphate and carbonate precipitate in the urine, the same apparently not being due either to motor insufficiency or hyperacidity of the stomach, since the stomach secretion was alkaline at night and early morning.

Soetbeer (1902) made a very satisfactory comparison of a child exhibiting phosphaturia with one in normal condition. The phosphorus in the urine was about the same, slightly higher with the healthy child, but the lime more than two-and-a-half times as much in the urine of the patient as in that of the control. The phosphorus of the feces was the same in both cases, as also was the lime insoluble in water but soluble in hydrochloric acid, while the water-soluble lime was 0.037 gm. in the patient and 0.310 gm. in the control; thus the essential difference in these cases was that the control had excreted water-soluble lime into the intestine, while the patient had excreted the same into the urine, the difference apparently being due to intestinal catarrh in the pathological case.

Soetbeer and Krieger (1902) reported a case of phosphaturia where the ratio P_2O_5:CaO was sometimes 1.5 or 2 to 1 instead of 12 to 1, the normal relation, while the urinary elimination of lime rose to almost 0.7 gm. daily, the normal being about 0.2 gm. See also Panek (1900) and De Lange (1903).

Gouraud (1903) investigated the ratio of P to N in the urine of patients suffering from pneumonia, typhoid fever, rheumatism, cerebrospinal meningitis, tubercular meningitis, diabetes, neurasthenia and false and true phosphaturia. No account was taken of food or feces phosphorus. Gouraud distinguishes between false phosphaturia, ordinarily due to alkalinity of the urine, and true phosphaturia, due especially to (1) dyspepsia, especially hyperchlorhydria, which produces only a minimum increase, (2) tuberculosis, with phosphaturia as a complication, (3) diabetes, in its more serious forms, and (4) nervous states, particularly neurasthenia.

Von Düring (1905) studied 60 cases of phosphaturia. He concluded that cases of phosphaturia, attributed to neurasthenia, were actually caused by urethritis and prostatitis, the neurasthenia being secondary, and sometimes late in appearing. Von Düring explains it by the idea that the whole urogenital tract is inflamed by inflammation of any part, the parenchyma of the kidneys thus becoming impaired. Albuminuria was found often to accompany phosphaturia.

Moll (1905) describes a case of hysteria combined with intestinal catarrh in a child 5½ years old. A symptom of the case was an abnormal amount of calcium phosphate in the urine. While in this condition the child lost 2.5 kg. in weight in 2.5 months. After a change of diet, and an avoidance of lime-rich foods there was an improvement in general health, and a gain in weight of 2 kg. in 1½ months, the urine being normal. With a return to the original diet came a return of the old symptoms, and an increase of calcium and phosphorus, especially the former, in the urine. The diet was once more changed to fat, meat, sugar and fruits, thus avoiding lime, with the result that the urine became normal, and the nervous and digestive disturbances disappeared.

Moll (1909) published an extensive report of further studies of this same subject, having reference to breast-fed infants. In this study he made a comparison of the composition of the urine of healthy infants and those suffering from defective digestion, the following are a part of the conclusions from parts I and II of the report:

The urine of healthy breast-fed infants contains no phosphorus, or only traces.

The dyspeptic infant excretes more or less phosphorus through the urine. This amount may be decreased by a short fasting period (24 hours), a reduction of the number of feedings, or artificial evacuation of the intestine. If the trouble is relieved the phosphorus content of the urine decreases; if it continues the phosphorus increases.

In inanition, in the ordinary sense of the word, if not carried too far, no phosphorus, or only a trace is excreted in the urine of the healthy child.

If a breast-fed child gains in weight and shows no sign of illness, and has no phosphorus in the urine, then it is healthy.

If the breast-fed infant gains in weight, and with insufficient food intake shows no phosphorus, or only traces, in the urine, it is starved.

If the child does not gain or lose in weight, and, with apparently insufficient nourishment, excretes large quantities of phosphorus in the urine, it has a digestive disorder. Thus the content of the urine in phosphorus is a gauge of the condition of the infant.

Loss in weight and a high percentage of phosphorus in the urine run in a parallel way; also gain in weight and a low percentage of phosphorus in the urine.

The same milk reacts differently on different children. It is possible then to determine the effect on the child of a change of milk by testing the urine (24 hours) for phosphates. If benefit has been received the urine will show a considerable decrease in phosphorus.

In part III of this article Moll discusses acute gastroenteritis in infants, and submits experimental data showing the effect of treatment on the phosphorus of the urine.

In the height of the disease there is a high percentage of phosphorus in the urine, which is quickly decreased by stopping the food intake, and substituting a water diet. These low values persist during convalescence. When breast-feeding is resumed the values of urine phosphorus increase again. The tolerance of the organism toward new food is measured by the urine analysis. The organic phosphorus present in severe stages of the disease disappears with the decrease of total phosphorus in the urine.

In cases which have a fatal termination this fasting therapy does not produce the above results, that is, improvement, in general, accompanied by decreased urine phosphate.

Organic phosphorus in the urine of the breast-fed child is to be regarded as a pathological symptom.

Von Moraczewski (1905) gave attention to the balance of acid and basic elements in pathological urines. His table as published is in need of recalculation. A part of the conclusions are as follows:

The chronic phosphaturia which does not show the clinical symptoms of neurasthenic phosphaturia, or of the phosphaturia of children, is characterized by an abnormal relation of phosphorus and calcium elimination in the urine, in that, coincident with a decrease of lime salts there is an increase, though small, of phosphorus.

By treatment with alkalis the elimination of the metalloid ions (chlorine, sulphur and phosphorus) is relatively more favored than that of the metal ions, by which the relative elimination returns to the normal. One and the same individual may have this form of phosphaturia and gout; that is, (a) may show phosphaturia alternating with oxaluria or gout; (b) may suffer generally with phosphaturia and then with gout, or the reverse. Normal urine contains more acid ions than the urine of phosphaturia or gout.

Tobler (1905) published data on two cases of phosphaturia. As usual the lime in the urine was high, while the phosphorus remained within normal limits, but the lack of food analyses limits the use of the data.

Doctor (1906) says that phosphorus estimations show that it is incorrect to designate every case of alkalinuria as phosphaturia.

Langstein (1906) observes the presence of phosphaturia in cases of disease where there was not the usual excess alkali or excess removal of acid as a cause. He mentions sexual phosphaturia, due to a complication of diseases of the urogenital system; neurasthenic, causing reflex effects on kidney secretions; that form which von Moraczewski describes as associated with uric acid diathesis, and finally the juvenile form. Langstein describes in detail the nervous symptoms accompanying the juvenile form. He considers overnourishment on foods such as milk and eggs, which are rich in lime to be the cause, and found that dietetic changes on this basis caused marked improvement. In his cases there was no intestinal catarrh demonstrable. Langstein emphasizes the diversity of causes of phosphaturia.

Novi (1908) reports a reduction of the urinary phosphorus, in phosphaturia following antirabes treatment, from 69.11 percent of an intake of 2.457 gm. to 46.07 percent of an intake of 2.451 gm., plus 0.603 gm. P_2O_5 in the shape of phytin, the difference being ascribed to this phosphatic supplement.

Klemperer (1908), in an extended study of various phases of phosphaturia, found that doses of 0.3 gm. oxalic acid plus 3.0 gm. $NaHCO_3$ greatly decreased the absorptive power of the kidneys for calcium, as also did very small quantities of $HgCl_2$ (1 drop 3 times daily of a 5-percent solution, in all 1.0 mg. in 24 hours).

PHYTIN THERAPY

This subject is discussed in connection with normal phytin metabolism; see p. 315.

RACHITIS

Rachitis has been known for a very long time; at least it was described by Glissonius in 1650. It is a disease of infants which involves phosphorus metabolism, especially through its effects upon the bones, but also apparently in other ways as well. In the literature of the subject much prominence is given to the element calcium, but we may bear in mind the fact that one could as consistently put the same emphasis on phosphorus, for these two elements are used together in the tissues most involved in rachitis.

In rickets calcification of the bones is irregular; areas of partial ossification lying between areas of greatly enlarged cartilage cells. The bone is deeply imperforate by projections into it of both marrow and periosteum, and the marrow spaces are enlarged and irregular. Absorption of formed bone is not prominent as in osteomalacia, but, rather, a failure of the osteoid tissues to calcify.

Associated with rickets there are often gastrointestinal disorders, and anaemic changes in the blood. The blood alkalinity, however, was found normal by Stöltzner.

The largest part of the literature of rachitis has to do with its etiology. This aspect of the problem, however, remains unsolved. Among the possible causes, lack of calcium in the food, deficient absorption of calcium, and acid intoxication, none fits the facts in a thoroughly satisfactory manner. From an enormous literature, of which we do not attempt to review the whole, the following are some representative fragments.

Among the earlier papers which we have seen are those of Gobley (1844, 1846), who used ray's liver oil with success in rickets, Virchow (1853), who histologically distinguished rickets from osteomalacia, G. Wegner (1872), who studied the effects of the element phosphorus repeatedly administered in small doses, and suggested the probable benefit from such treatment in rachitis, Heitzmann (1873), who thought he produced rickets and osteomalacia with lime-poor food and lactic acid, and Roloff (1875a, 1875b, 1879), who also produced and cured artificial rickets, and considered it actual rickets, which he thought due to lack of phosphorus in the food.

Seeman (1879) considered rickets as caused by deficient absorption of lime, due to digestive disorders originating in a subnormal hydrochloric acid content of the gastric juice.

Zander (1881) also had the idea of a deficiency of hydrochloric acid in the gastric juice, and considered this due to an excess of potassium and phosphorus in the mother's milk causing an undue elimination of sodium and chlorine. These observations were based on the study of the composition of the milk of the mothers of normal and of rachitic children.

E. Voit (1880) recognized the futility of feeding calcium salts in actual rickets, and recommended attention to the gastrointestinal disorders often accompanying rickets, considering these the cause, and their relief the cure.

Kassowitz (1881, 1884a, 1884b, 1886) experimented with phosphorus therapy in rickets. He considered that it reduced the morbidly increased vascularization of the osteoid tissue from which result the characteristic bone conditions. Kassowitz experimented with many thousands of cases (1890) and recommended "lipanin," olive oil and phosphorus. Other statements of his ideas and results are found in his publications of 1901, 1910, 1912. He expresses the idea that rachitis is not due to lack of lime in the food. Phosphorus,

he finds, causes hardening of the bone through the laying on of lime salts, and he speaks of rickets as involving an abnormal increase of tissue building, and an abnormal fullness of blood in the bone-making tissues.

J. Cohnheim (1882) published an extended discussion of the disease, as also did Pommer (1885), who considered it as originating outside the skeleton.

Baginsky (1882) studied demineralization by lactic acid in connection with rickets.

Anna Schabanowa (1889) reported successful use of phosphorus in rickets.

Korsakov (1892) could not cause rickety conditions by feeding lactic acid. Phosphorus therapy caused varying results, some successful, others not. Strontium salts used in rickets caused a certain amount of ossification. Cremer (1891), however, found that strontium phosphate would not prevent the appearance of rickety symptoms in a dog on a low calcium diet, though it was deposited to some extent in the bones.

Brubacher (1890) shows that in congenital rickets the body is characteristically poor in ash. On the dry, fat-free basis calcium and phosphorus are both markedly deficient, the former decidedly more so than the latter. The analysis of the ash shows calcium quite deficient, and phosphorus only slightly so. Magnesium seems not to vary in an important way. Brubacher agreed with Kassowitz in the belief that organs other than the bones were not subnormal in calcium.

Herter (1898) experimented with fat-free rations on swine, having in mind the alleged low fat content of the milk of women whose children have grown rachitic on the mother's milk, and also the occurrence of rickets in children fed largely on condensed milk. He concluded that fat starvation causes a very imperfect absorption of phosphorus from the intestine; but since complete balance data were lacking we must suspend judgment on this matter. There was nothing resembling or suggesting rickets, however, in the results from the fat-free rations.

Rüdel (1893b) satisfactorily demonstrated that lime was absorbed from the carbonate and the acetate, and was also excreted, by rickety children, in a normal manner.

Chabrié (1894, 1895) developed an interesting theory of the causation of rickets by the interference of lactic acid in the normal formation of collagen from chondrin, a process necessary to normal ossification, and also the interference of lactic acid with the normal precipitation of calcium phosphate and calcium carbonate in bone by

the fixation by lecithin of the carbonic acid holding them in solution, lecithin thus being necessary to normal utilization of inorganic phosphates. For details see the original. He also explained the partial replacement of calcium of the bones by magnesium, in osteomalacia, by reference to a different relation to lecithin.

Flieger (1897) reported many unsuccessful attempts to cure rickets with phosphorus in cod-liver oil. The reason for his failure is not apparent.

Zweifel (1900) advanced the theory that deficient hydrochloric acid of the gastric juice, as caused by lack of common salt in the diet, interfered with the solution of calcium salts, and so caused rickets; and Delcourt (1899) stated that he had produced in bones lesions similar to those of rickets by means of potassium phosphate.

Leichnam (1903) found phosphorus, calcium, magnesium and chlorides all above normal, and urea below normal, in the urine in rickets, indicating a profound state of denutrition.

W. Stoeltzner (1903) reports negative results from phosphorus therapy in much complicated cases. He recommended phosphorus, however, (1904) to be administered in cod-liver oil, and suggested as a cause of rickets the functional insufficiency of some organ analogous to the thyroid gland.

Bürger (1904) reports benefit from the use of protylin; Fürst (1904), from the use of phytin; Lepski (1905) reported negative results from phosphorus in cases complicated by severe general illness; Pfaundler (1904) observed no difference in calcium ion absorption by finely ground bone and cartilage of normal and rickety children, which, so far as it goes, argues against the idea of an inability of rachitic bones to absorb calcium salts in the normal manner.

Birk (1909) reports that phosphorized cod-liver oil increased mineral retention in rachitis, and that calcium retention varied inversely as fecal soap formation. (See table below.)

CALCIUM AND PHOSPHORUS METABOLISM—HEALTHY AND RACHITIC CHILDREN

Diet	Condition	Child	CaO intake Grams	CaO retention Grams	Percent CaO retention	P intake Grams	P retention Grams	Percent P retention	Length of period
Without phosphorized cod-liver oil	Healthy	Sch.	2.175	+0.942	43	4.654	+0.995	21	3 days
		K	2.600	+0.515	20	4.517	+0.834	18	"
	Rachitic	T	1.417	+0.021	2	1.862	−0.159	..	"
		F	1.629	−0.135	..	2.238	−0.110	..	"
With phosphorized cod-liver oil	Healthy	Sch.	2.726	+1.200	44	5.716	+1.951	32	"
		K	2.390	+0.573	24	4.158	+0.708	17	"
	Rachitic	T	1.247	+0.120	10	1.504	−0.131	..	"
		F	1.694	+0.111	7	2.386	+0.201	8	"

In these data we see no positive evidence of an increased retention of phosphorus, as a result of the administration of phosphorized cod-liver oil, though there seems to have been an improved retention of lime.

Aron (1908) found the milk of the mothers of rachitic children to be subnormal in lime, as also did Ramacci (1910).

W. Cronheim and E. Müller (1908) found, in balance experiments on normal and rickety children, that nitrogen assimilation and absorption was normal in the latter, and their experiments showed nothing markedly abnormal about the mineral balances, all of which were positive.

Dibbelt (1908, 1909) considered, in view of the completeness of utilization of the calcium normally present in woman's milk, that under abnormal conditions, it is likely that the calcium content is often deficient. He also concluded that feeding with cow's milk must often lead to calcium-loss through lower retention, especially through the gastrointestinal disorders prevalent at weaning time. Dibbelt considers that the low content of infants' food in calcium phosphate is a predisposing factor in the development of rickets. He puts much emphasis on gastrointestinal disorders as a causative factor.

The following balances from Dibbelt's work are of interest, because, in the light of Schabad's conclusions, they may be considered to represent a case, not of actual, but of pseudorachitis, since there were positive nitrogen and phosphorus balances coincident with a marked loss of calcium, which last became strongly positive simply through a change of food.

DAILY NITROGEN, CALCIUM AND PHOSPHORUS BALANCES WITH NORMAL AND RACHITIC INFANTS—Grams

Subject		N	CaO	P_2O_5	Diet
No. 1. Healthy; age 25 days	Intake	2.0320	0.6098	0.7913	Cow's milk; after change from mother's milk
	Outgo	1.5419	0.9022	0.8840	
	Retention	+0.4901	−0.2924	−0.0933	
	Retention per kg. body weight	+0.1223	−0.0731	−0.0248	
No. 2. Rachitic; age 7 months	Intake	4.1310	1.1070	1.4870	Specially prepared buttermilk
	Outgo	2.7885	1.4460	1.4227	
	Retention	+1.3455	−0.3390	+0.0623	
	Retention per kg. body weight	+0.2790	−0.0704	+0.0123	
No. 2. Rachitic; same subject as above but at a later date	Intake	5.0400	1.5030	1.9058	Undiluted whole cow's milk
	Outgo	3.1546	0.7495	1.8256	
	Retention	+1.8854	+0.7555	+0.0802	
	Retention per kg. body weight	+0.3840	+0.1547	+0.0160	

Dibbelt reported success in increasing the calcium content of woman's milk from 0.575 to 1.852 parts per 1000 by adding calcium salts to the food, and that he decreased the calcium content of dog's milk from 4.56 to 1.94 parts per 1000 by use of a ration low in calcium, these results being in marked contrast to the prevailing trend of evidence on this matter.

Bahrdt and Edelstein (1910) submit data showing the calcium content of normal woman's milk to be 0.0426 percent CaO, and that of the milk used by rickety infants (sustained by many collected figures) as 0.0315 percent CaO. Efforts on the part of the authors to increase the calcium content of the milk of a woman met with apparent success in the feeding of calcium carbonate, but with calcium lactate the results varied widely, from much below the normal to a little above.

Lauxen (1909) studied elemental phosphorus administration to young normal dogs, having in mind the bearing of the results on phosphorus therapy in rachitis. Phosphorus was shown to affect the character of the leucocytes in a manner opposite to that of rachitis. In the bones there was a pronounced hardening, with a decrease of osteoclasts. New bone formation was of a type characteristic of phosphorus action, and decreased the marrow spaces. Histological observation led to the conclusion that phosphorus has a paralyzing effect on the bone cells, decreasing both apposition and resorption, but leaving a residual balance in favor of apposition. The spleen was much enlarged, possibly on account of taking up blood-formation to compensate for restriction of this function in the bone marrow.

Dibbelt (1909), in experiments on dogs with experimental rickets, concluded that human rickets is due to anomalies of absorption and secretion. A late expression from Dibbelt (1910a) is a theory to the effect that the cause of rickets is an abnormal amount of calcium-precipitating compounds, such as phosphorus, from decomposition of undigested casein, and carbonates from carbohydrate fermentation, in the intestine.

Flamini (1907) submits calcium balance experiments with both normal and rickety children under phosphorus therapy. With the former there was a change from a calcium retention of 37.4, 36.3 and 26.6 percent of the intake to 37.8, 46.1 and 36.5 percent after 12-15 days of phosphorus treatment, while with rickety children the increase was from 59.7, 56.8 and 55.7 percent to 68.2, 72.6 and 61.1 percent after 12-20 days of phosphorus therapy.

Gassmann (1910) finds that lime, phosphoric acid and carbonic acid all decrease in amount in rachitic bones, together with a loss of water. The relations $Ca:PO_4:CO_3$ are about the same for normal and rachitic bones. Magnesium is considerably increased in rachitic bones.

ANALYSIS OF NORMAL AND RACHITIC BONES—(Gassmann, 1910)

	Normal ribs Mean of 2 computed	Rachitic ribs Mean of 2 computed
	Percent of dry substance	
Loss on glowing	37.14	42.73
Ca	24.40	21.48
Mg	0.10	0.64
PO_4	33.56	30.38
CO_3	3.11	2.76
Cl	0.43	0.45
K	0.30	0.31
Na	0.64	0.73
Sum	99.68	99.48

Aschenheim and Kaumheimer (1911) find calcium and phosphorus diminished in the muscles of rachitic children, by comparison of their figures for pathological cases with Tobler's figures for the normal. In 6 cases the phosphorus in the muscle varied from 0.3849 to 0.6485 percent, the normal being given as 0.325 percent. In these same six cases the calcium varied between 0.0255 and 0.0570 percent, while the normal is given as 0.0650.

Schabad has conducted a most excellent series of studies of calcium and phosphorus metabolism in rachitis which contributes much to our understanding of the subject. A large part of Schabad's study has centered in the use of elemental phosphorus in the treatment of this disease. A comparison of its action on rachitic and normal children (1907) shows that in rickets phosphorus assists in the absorption and retention of calcium, and also changes the composition of the bones toward the normal, but that in health it produces no such effects. See also Schabad (1908) and (1909a). Phosphorus administered with cod-liver oil has given best results in increasing retention of both calcium and phosphorus, both substances taking part in the improvement (1909b), while with the addition of calcium acetate a still larger retention of both calcium and phosphorus is brought about.

Calcium citrate and calcium phosphate added to phosphorized cod-liver oil, not only are not retained, but they decrease the phosphorus retention. The acetate, however, as above noted, had the

opposite effect, and also brought about an increased nitrogen retention; though at the same time both the nitrogen and fat of the feces were increased (1910a, 1910b).

Lipanin, olive oil and sesame oil cannot replace the cod-liver oil in the treatment of rickets (Schabad and Sorochowitsch, 1911a), and the repeated heating of cod-liver oil to 100° for an hour does not destroy its beneficial action in rickets (Schabad and Sorochowitsch, 1912).

Schabad submits many data to show that only the maximum normal calcium content of human milk can cover the real needs of the infant for calcium, and that there are doubtless many occasions when it is insufficient (1909d). That a deficiency of the milk in calcium should be the cause of rickets he considers not to be excluded by his studies. Rickets is histologically, but not otherwise, distinguishable from the experimental or natural malnutrition of the bones of domestic animals, which Schabad calls pseudorachitis. In order to identify a condition in human beings parallel with the pseudorachitis of the domestic animals Schabad assumes that both actual and pseudorachitis exist in human beings without our being able to distinguish them.

There is conflict in the evidence as to whether or not the calcium of tissues other than bones is subnormal in rachitis. Perhaps the difference in observations on this point is due to the confusion of actual and pseudorachitis.

Schabad finds the calcium content of the milk of the mothers of rickety children slightly lower than normal, and the content of organic nutrients somewhat above normal, so that the calcium content as related to the calorific value is considerably below the normal. He finds, however, that rachitis can occur with a maximum calcium content of the milk, so that it is impossible to consider a deficiency of the milk in calcium as the only cause (1909e, 1911a) though is has not been so definitely related to any other condition. It has been found impossible to increase the calcium content of woman's milk by feeding.

The effect of rachitis on phosphorus excretion is shown by the following table from Schabad (1910d) (page 574).

For all groups the phosphorus excretion in rickets is distinctly higher than in health, and amounts in the urine are smaller. In developing rickets calcium and phosphorus excretion increase together, with excess of the latter, and the increased phosphorus excretion usually exceeds the bone-equivalent of the accompanying calcium, so that participation of other phosphorus-rich tissues is

apparent. The increase of phosphorus excretion is in the feces, the urine phosphorus decreasing toward the normal, and the normal excess of urine phosphorus over feces phosphorus is changed to an excess of feces phosphorus over urine phosphorus. In convalescence, the total phosphorus excretion is subnormal, and the normal excess of urine phosphorus over feces phosphorus returns.

AVERAGE DAILY PHOSPHORUS EXCRETION BY RICKETY AND HEALTHY CHILDREN OF THE SAME AGE, AND ON THE SAME DIET

Diet	Condition	P_2O_5 excretion per kilo per day		Relative P_2O_5 excretion, in percent of amount given		Partition of P_2O_5 excretion		Excess in feces in relation to $Ca_3(PO_4)_2$	
		Total Grams	In urine Grams	Total	In urine	Urine	Feces	CaO	P_2O_5
Breast fed	Healthy, 4-5 mos.	0.023	0.018	65.3	52.8	80.6	19.4	64.8	....
	Progr. rickets, 5-13 mos.	0.034	0.021	122.2	72.2	60.8	39.2	52.8	....
Infants on cow's milk	Healthy, 3-6 mos.	0.214	0.119	79.7	45.1	65.2*	34.8	22.8	....
	Progr. rickets, 5-8½ mos.	0.186	0.077	94.6	39.3	39.3**	60.7	14.1	....
Older children on mixed diet	Healthy, 4-5 yrs.	0.159	0.102	80.3	51.5	64.4	35.6	22.	....
	Progr. rickets, 4 yrs.	0.091	0.040	102.1	44.9	44.1	55.9	....	39.8
Developed rickets, 1 yr. 5 mos. to 2 yr. 7 mos.		0.178	0.069	71.8	27.5	38.2	61.8	(16.5)	23.3
Convalescent, 2½-8 yrs.....		0.103	0.077	65.5	48.7	74.4	25.6	25.6	(64)

* We figure this to be 55 6, and the feces figure 44.4.

* * We figure this to be 41.4, and the feces figure 58.6.

The calcium balance (1910c) varies during the course of a case of rickets from negative or subnormally positive in the progressive stage, to decided retention, which begins some time before the clinical manifestations of improvement, and later, in convalescence, to a retention of two or three times the normal amount, which, on complete recovery, falls again to the normal.

Increased excretion of calcium in the progressive stage of the disease is through the feces; calcium excretion at this stage is subnormal in the urine, and in the convalescent stage above normal in the urine. These facts, Schabad states, rule out the acid theory of the cause of rickets.

Schabad finds that increased calcium excretion in the feces increases the phosphorus retained in the intestine, and conversely that increased phosphorus excretion in the feces increases the calcium retained in the intestine; therefore, since in rickets the feces phosphorus exceeds the bone-equivalent of the feces calcium, the increased excretion of phosphorus, and not of calcium, is the primary factor.

Schabad (1909c) finds that in advanced stages of rickets the relation of calcium to phosphorus in the bones changes, the calcium decreasing, and the phosphorus increasing, whereby the normal relation of calcium to phosphorus of 100:75-85 is changed to 100: 70-75, the decrease in total ash affecting the calcium more than the phosphorus.

Cattaneo (1909) also notes departure from the normal composition of the bones in rachitis, especially in the direction of a relative increase in magnesium.

Rickets complicated with tetany, Schabad (1910-11) finds not to differ as to calcium and phosphorus metabolism from uncomplicated rickets.

Schabad states (1909e) that in pseudorachitis there is no such excess of phosphorus over calcium in the feces as in true rickets, but rather, an excess of calcium over phosphorus, a fact which suggests a different degree of participation of organs other than the bones in the production of the mineral losses in these diseases.

As shown by the table below, Ogata (1911-12) finds the calcium phosphate as well as other mineral salts of the bones much lowered by rickets. Different proportionate reduction in the amounts of the several salts result in an altered relation of one to another in the bone. There was marked increase of collagen and fat.

ANALYSES OF NORMAL AND RACHITIC BONES
Ogata (1911-12)—Percent

	Bones of 2-mos.-old healthy child		Bones of patient having rachitis*				
	Tibia	Ulna	Femur	Tibia	Humerus	Ribs	Vertebrae
Inorganic substance	65.32	64.07	20.60	33.64	18.88	37.19	32.29
Organic substance	34.68	35.93	39.40	66.36	81.12	62.91	67.71
Calcium phosphate	57.54	56.35	14.76	26.94	15.60	.....	.....
Magnesium phosphate	1.00	1.00	0.80	0.81	.....	.....	.....
Calcium carbonate	6.02	6.07	3.00	4.88	2.66	.....	.....
Soluble salts	0.73	1.66	1.02	1.08	2.62	.....	.....
Collagen	33.86	34.92	72.20	60.14	81.22	.....	.....
Fat	0.82	1.01	7.20	6.22	.....	.....	.....

* The age of the rachitic patient was not stated.

Schabad (1911b, 1911c) reported unfavorable results from the use of the phosphorized cod-liver oil treatment in two cases of so-called late rickets.

Schabad and Miss Sorochowitsch (1911b) studied calcium, phosphorus, nitrogen and fat metabolism in rachitic infants as affected by various preparations of cod-liver oil and inorganic salts. The phosphorized cod-liver oil alone was found sometimes to be without beneficial effect. The most liberal calcium retention resulted from the use of calcium acetate with cod-liver oil emulsion. Phos-

phorus was retained in considerable quantity from cod-liver oil emulsion with hypophosphites of sodium and calcium.

C. Meyer (1913) found in metabolism experiments with rickety infants that phosphorized cod-liver oil caused a marked reduction in the feces phosphorus, and improved retention of this element.

Gessner (1913) considers that rickets is the result of a disturbed fat metabolism, among the causes of which are deficiency of fat in modified milk, a retarded state of metabolism generally, and the prevalence of acid-reacting metabolites in the blood and lymph. He believes that the efficiency of phosphorized cod-liver oil in the treatment of rickets is due to its ready emulsification and absorption, the presence of phosphorus facilitating its oxidation. Gessner likens this relation of fat and phosphorus to that naturally existing in the phosphatids of the body.

Schloss (1913a, 1913b) reports results from metabolism studies on a breast-fed infant under treatment for rachitis. The calcium balance was very unfavorably influenced by phosphorized cod-liver oil alone, but with calcium acetate added the balance became and continued to be strongly positive; the phosphorus balance was affected much as was that of calcium, though in much lower degree; a moderate retention of magnesium in the fore-period became strongly negative under the influence of phosphorized cod-liver oil and of calcium acetate; phosphorized cod-liver oil diverted alkalis from urine to feces, and the addition of calcium acetate led to large loss of alkalis.

In a later study Schloss (1914a) confirmed previous observations on the ineffectiveness of phosphorized cod-liver oil alone, and the effectiveness of the oil and calcium salts together on the calcium balance. It was found, further, that the calcium salt alone is ineffective, and that two calcium-casein preparations are of value in combination with phosphorized cod-liver oil.

Regarding the phosphorus metabolism, the introduction of calcium acetate increased the feces phosphorus; the addition of cod-liver oil slightly improved the balance, while the oil alone caused only a different distribution of the phosphorus elimination. An improvement of the phosphorus balance comparable with that of calcium was first seen when the calcium caseonphosphate and plasmon were used.

In a third paper Schloss (1914b) reported once more that phosphorized cod-liver oil has an unfavorable influence on nitrogen, calcium and phosphorus metabolism, and also that $CaHPO_4$ with phosphorized cod-liver oil very greatly improved the calcium and especially the phosphorus balance. Plasmon and $CaHPO_4$ were said to have identical effects on calcium and phosphorus metabolism.

Kochmann (1912), in balance experiments on dogs, studied the effect of elementary phosphorus on calcium metabolism. The phosphorus was administered in quantities of 1 to 2 mg. daily. By using larger doses than is possible in human medicine he obtained positive results such as have not been obtained from the use of phosphorus without cod-liver oil with human beings. The effective quantities equalled or exceeded the toxic dose without exercising an influence beyond the time of administration.

During the use of the phosphorus there was a regular and continuous reduction in the preëxisting positive phosphorus balance until it finally became a minus figure. The calcium balance, which was negative during the preliminary feeding, was considerably improved during the phosphorus therapy, but did not become positive until calcium chloride and phosphorus were given together, which produced marked retention of both calcium and phosphorus. Magnesium metabolism ran parallel to nitrogen metabolism and was not influenced by phosphorus therapy.

Ribbert (1913) reports a more or less complete destruction of the cartilage cells in rachitis. From the finding of these cell-changes in light cases and at the onset of the disease, he concludes that this condition is a primary one, apparently due to some toxic substance which hinders calcium deposition in cartilage and bones. Ribbert considers the origin of this causative toxic substance to lie in metabolic disturbances resulting from wrong feeding.

Kassowitz (1913) states his own experience and also cites results of others showing that cod-liver oil is not essential to the utilization of phosphorus in rickets, that phosphorus is of value in combination with other oils, and of some value alone. Kassowitz cites cases in which prolonged treatment with cod-liver oil alone was not beneficial. He does not believe that the calcium balance points the way either to the cause or treatment for rachitis.

See also Dibbelt (1913), Diesing (1913), and Bamberg and Huldschinsky (1913).

The etiology of rachitis remains an unsolved problem.

THE THYROID GLAND IN RELATION TO PHOSPHORUS METABOLISM

The thyroid gland exercises important control over metabolism, especially of nitrogenous compounds. Ingestion of thyroid gland substance increases tissue katabolism, while deficiency in the thyroid causes cessation of physical, mental and sexual development, and also retards ossification of epiphyseal cartilages, leading to the characteristic deformity of cretins. Oxygen consumption and carbon

dioxide secretion are diminished, and metabolism generally is greatly depressed. There is considerable evidence that the disturbance of functions is due to toxic products of protein metabolism, which, through the agency of the thyroid secretion, are normally rendered innocuous.

The thyroid stands in close relation to the reproductive functions, as is shown by its hypertrophy at the time of sexual maturity, during the menses, and during gestation and lactation. Myxoedema and cretinism are associated with subnormal thyroid secretion; while there is some evidence that exophthalmic goiter depends on excessive thyroid secretion.

Ord and White (Brit. Med. Jour. 1893, 2, 216), studying thyroid treatment in myxoedema, note a slight increase in phosphorus excretion, though Houghhardy and Langstein (Jahrb. für Kinderh. 61, 634, 1905) observed a retention of calcium and phosphorus, apparently due to the growth of bone in a growing child.

Roos (1895) found in experiments on healthy animals that the administration of thyroid gland substance in large doses caused a marked increase in nitrogen elimination (much more than the nitrogen so introduced) lasting for several days, and also increased sodium chloride and phosphorus elimination. The increased elimination of chlorine lasted only 2 or 3 days, and then sank abruptly to a markedly subnormal amount, while the increased phosphorus elimination, like that of nitrogen, persisted.

The administration of thyroid substance to a dog, deprived of the thyroid gland, increased the nitrogen and chlorine elimination to a greater degree than when given to a normal animal, but the phosphorus elimination remained considerably below normal.

Roos concludes that the thyroid gland has a decided influence on phosphorus metabolism, the nature of which is as yet obscure, though he notes evidence sustaining the idea that phosphorus assimilation requires the assistance of a secretory product of the thyroid.

Bayon (1903) reported confirmation of the findings of others in such experiments, that broken bones heal less quickly and completely in animals from which the thyroids have been removed, and that administering thyroid-gland preparations to such animals favors the healing, though not entirely making up for the loss of the glands; also that such preparations favor healing of fractures in normal animals as well.

Scholz (1905) has made thoroughgoing studies of metabolism in three cretins, covering periods of 95, 95 and 117 days respectively, and including complete mineral balances. The work covers the

normal state of metabolism, and the modifications produced by the ingestion of thyroid tablets, and of 5 gm. trisodium phosphate per day. Scholz states that metabolism of cretins is to be regarded as sluggish. The urine is decreased, and uric acid, creatinin and sodium chloride are excreted in subnormal quantities; but urea, xanthin bases, ammonia and sulphur compounds appear to have normal values. The alkaline earths show increased excretion. The phosphorus retention is considerable, on a small intake, and does not increase proportionately with increased intake. There was nothing characteristic in the effects of thyroid treatment on phosphorus metabolism.

Aeschbacher (1905-6) studied the thyroid glands of 61 persons. He found the phosphorus content determined mainly by the richness of the gland in nuclei, but in part by the phosphorus content of the colloid. As noted by Kocher, there was generally a reciprocal relation between the quantities of phosphorus and iodine in the gland, due principally to the fact that glands rich in the iodine-containing colloid are relatively poor in cells. The thyroids of women were found larger and also richer in iodine, than the thyroids of men, while the phosphorus value reaches the higher figure in the thyroids of men. Diseases which cause circulatory disturbances cause a marked decrease in the iodine content of the gland, but for phosphorus this relation does not hold.

Saccone (1907) removed the thyroids and parathyroids from a dog, after which the urinary phosphorus rose to three times the previous amount. The feeding of a phosphatic diet containing liver, brain and sodium glycerophosphate did not bring about normal conditions, but instead, increased especially the organic phosphorus of the urine; the feeding of the normal diet, however, with the addition of thyroidin reduced the excretion of phosphorus to the original level.

Underhill and Saiki (1908) in the few urinary phosphorus estimations made in their metabolism study note a low phosphorus elimination "possibly indicating when considered with the low purin and allantoin excretion, a low rate of nuclear disintegration. A large output of purin-nitrogen and a low output of phosphorus were observed after the continued administration of large doses of thyroid tissue."

Soli (1909) finds that rabbits, if deprived of thyroids at a sufficiently early age, fail to develop the skeleton normally, while guinea pigs and chickens did not show this result so readily.

Bircher (1910) removed the thyroid glands from 6 rats of the same litter. To three of these he fed thyroidin tablets. The others were used as controls. The former showed much the more rapid calcification of the bones.

A. Juschtschenko (1911) observed that thyroidectomy reduced the nuclease content of young dogs.

Schäfer (1912) found that the addition of small amounts of thyroid tissue to the diet of white rats greatly increased the food consumption, especially in quite young individuals, with acceleration of growth, and retention of nitrogen. Phosphorus excretion is increased if the ingestion of thyroid is increased beyond a certain point.

A. I. Ushenko (1913) found that after thyroidectomy the ratio of phosphorus to nitrogen in the urine first increased and then decreased, synthetic processes suffering acute disturbance in tissues containing nitrogen and phosphorus.

A. S. Juschtschenko (1913) found in experiments on dogs that thyroidectomy causes a general disturbance of phosphorus compounds in the organs and tissues. There was general increase of the inorganic phosphorus of brain, heart, pancreas and liver, and general decrease of the total and organic phosphorus of the same. In the kidneys there was increase of the total phosphorus, generally both organic and inorganic; and in the serum organic and total phosphorus increased, while inorganic decreased.

Hyperthyroidism was also found to cause disturbance in the phosphorus distribution in the tissues, these disturbances being in some respects just the opposite to those observed in athyroidism. The organic and total phosphorus are decreased in brain, muscle and heart, but are increased in liver, kidney, pancreas and serum. Inorganic phosphorus was less in all the tissues than in the normal animal, a fact almost completely opposite to the results in thyroidectomy.

Confusion has resulted, in the study of the function of the thyroid, through the removal along with the thyroid of the parathyroids, or parts of the same, or through their injury. Further study will more sharply differentiate their functions.

Karl Dröge (1913) has recently reported experiments with young dogs in which observations were made on the effects during the suckling period of removal of thyroids, spleen or testicles. Six pups of a litter of eight were used. Dog I was killed about 12 hours after birth; dog II was kept as a control; the thyroid dogs I and II, the spleen-dog, and the testicle-dog were operated upon on the day

the weight had about doubled, the 10th day; all were suckled by the mother. On the 23rd day the thyroid-dog I was killed to allow better nourishment of the others; the remaining dogs were killed as soon as there was any tendency shown to take other food than the mother's milk, the 28th day. The bodies were analyzed as a whole for moisture, fat and ash, and for nitrogen, calcium, magnesium and phosphorus in the fat-free dry substance and in the ether extract. We quote but two of the 44 tables of results given. Conclusions should await results with more individuals.

LIME, MAGNESIUM AND PHOSPHORUS CONTENT IN RELATION TO NITROGEN (Dröge, 1913)

Dog	Day of operation	Day killed	Nitrogen content Gm.	To 1 gm. nitrogen		
				CaO Gm.	MgO Gm.	P_2O_5 Gm.
Dog I	....	1st	6.87	0.31	0.003	0.43
Dog II	....	28th	30.63	0.49	0.008	0.60
Thyroid-dog I	10th	23rd	21.85	0.56	0.008	0.46
Thyroid-dog II	"	28th	17.06	0.44	0.008	0.62
Spleen-dog	"	"	19.48	0.74	0.004	0.67
Testicle-dog			35.34	0.52	0.005	0.54

PHOSPHORUS CONTENT IN FAT-FREE DRY SUBSTANCE AND IN ETHER-SOLUBLE SUBSTANCE (Dröge, 1913)

Dog	P_2O_5 in fat-free dry substance			P_2O_5 in ether-soluble substance			Total P_2O_5
	Weight of fat-free dry substance	P_2O_5	P_2O_5	Weight of ether-soluble substance	P_2O_5	P_2O_5	
	Grams	Percent	Grams	Grams	Percent	Grams	Grams
Dog I	61.1372	4.85	2.965	10.6278	?	?	2.965
Dog II	277.70	6.51	18.078	280.507	0.09	0.252	18.330
Thyroid-dog I	193.72	5.09	9.860	208.570	0.14	0.292	10.152
Thyroid-dog II	146.27	7.16	10.473	255.656	0.045	0.115	10.588
Spleen-dog	182.51	7.01	12.794	178.810	0.11	0.197	12.991
Testicle-dog	324.70	5.81	18.865	312.977	0.07	0.219	19.084

MORBUS BASEDOWII—EXOPHTHALMIC GOITER

Scholz (1895) conducted a complete balance experiment with a woman suffering from exophthalmic goiter, and with a healthy person on the same treatment for comparison, two periods of 3-5 days with each subject, one without treatment, and the other with dried thyroid gland substance.

Without treatment the goiter patient stored 7.437 gm. nitrogen and 1.06 gm. P_2O_5 per day; with thyroid treatment the nitrogen storage was 7.09 gm. per day, while the P_2O_5 balance fell from +1.06 to —2.09 gm.

Under thyroid treatment the nitrogen storage with the healthy subject fell from +3.76 to +2.64 gm., while the P_2O_5 balance fell from —2.996 to —3.831 gm.

There was not any great increase of phosphorus elimination in the urine with either subject, but in the feces the phosphorus elimination of the goiter patient was increased 10-fold, and that of the healthy subject about 25 percent. Since there was no such increase of nitrogen outgo as of phosphorus it was evident that the latter was due to phosphate rather than nuclein katabolism.

Von Noorden mentions the similar result of thyroid treatment on nitrogen metabolism by Hirschlaff (Zeit. klin. Med. 36, 200, 1899), and, on the other hand, the greatly increased excretion of nitrogen as observed by Matthes (Verhandl. der Cong. f. inn. Med. (1897), 232) and by David (Zeit. Heilkunde 17, 439).

That the behavior of Scholz's patient under thyroid treatment was typical seems not yet to have been demonstrated, though Roos (1895) and others obtained similar results, though less marked, in experiments with animals.

Berkley (1908) is said to have administered an alcoholic solution of lecithin in cases of exophthalmic goiter with strikingly favorable results. Berkley used this solution for alternate weeks with glycerophosphates, quinine and gentian, but with unfavorable results from the glycerophosphates. With lecithin there was gain in weight and relief from nervous symptoms, while with glycerophosphates there was loss in weight, and increase of nervous phenomena. Lecithin treatment was stated to be out of place with a disturbed digestion, and not of value without the assistance of a milk diet.

Tschikste (1911) considers, as a result of a metabolism study, that the iodin-free nucleoprotein which Oswald isolated from the thyroid has an influence in exophthalmic goiter opposite to that of thyreoidin (iodothyrin). In this article Tschikste reviews many articles on this subject that we have not consulted.

TOXINS, ANTITOXINS AND PHOSPHORUS METABOLISM

Dalmastri (1901) studied phosphorus metabolism as affected by rabes antitoxin. Metabolism generally was considerably increased during the cure, as shown by an increased loss of nitrogen and especially of phosphorus, and by loss of weight. The period following showed a prompt return to normal, so far as nitrogen and body weight go, but a slow return as to phosphorus.

Dmitriewski (1900) determined the effects on metabolism in the dog of poisonous substances extracted from *Bacillus pyocyaneus* and *Bacillus coli communis*, and also of diphtheria toxin. In carefully controlled subcutaneous injection experiments, it was found that all three of these poisons led to increased nitrogen and corresponding phosphorus elimination.

Novi (1904) published balance data on phosphorus metabolism during antirabes treatment, both with the virulent and non-virulent material, and also with and without sodium glycerophosphate, the latter being administered in one period *per os*, and in another by injection. Beyond a slight increase of urinary phosphorus, under the influence of the antirabes treatment, the figures did not show any notable departures from the normal, though the author states that the cure by both the toxic and the non-toxic treatment caused a leucocytosis and a following or coëxistent leucolysis. See also Decroly (1898).

Lederer and Stolte (1911) made mineral analyses of human and of dog hearts under normal conditions and under the influence of diphtheria or scarlet fever toxins. The authors did not find that these diseases alter the composition of the heart.

TUBERCULOSIS

The effects of tuberculosis on phosphorus metabolism are of several kinds; (1) characteristic changes, both quantitative and qualitative, in the phosphorus-containing lipoids of the tissues, (2) pathologic retention and deposit of phosphates in the calcification of degenerative tissues, (3) deranged organic functions of the parts affected, which of course may be of most diverse character, (4) others due to the fever induced by this disease, (5) still others due to anaemia, and lastly, (6) those of general starvation. The relation of tuberculosis to phosphorus metabolism, therefore, is largely general and incidental, and little attention has been given to the matter, except in relation to diet. In times past much prominence has been given the idea of flooding the system with lecithin, as in the very liberal ingestion of eggs, and benefit derived from such treatment has often been ascribed in large part to the phosphorus compounds present. Lecithin and nuclein phosphorus have also had a place in the treatment of this disease by parenteral injection. At present, however, an appreciation of the greater importance of the environment and general management has detracted emphasis from this particular dietetic consideration.

PHOSPHORUS METABOLISM IN TUBERCULOSIS

Passing over the earlier work referring to this matter, we note Mitulesco's (1902) observation that in times of hemorrhage from the lungs in tuberculosis there is a decrease of urinary nitrogen and phosphorus. In a later article (1903a), he reports complete nitrogen and phosphorus balances on four cases of tuberculosis. Three were given tuberculin treatment; the fourth hygienic and dietetic treatment only. The last mentioned patient improved slowly, and the positive nitrogen and phosphorus balances were increased. The three patients on tuberculin treatment were further advanced in the disease, all showing negative nitrogen and phosphorus balances. Under this treatment these balances all became positive, the improvement being greater than with the other case.

In another paper Mitulesco (1903b) reports nitrogen and phosphorus balances on eight cases of tuberculosis. In general the loss of nitrogen and phosphorus in the urine was excessive, and the balances negative. There was a high content of organic phosphorus in the urine. The nitrogen and phosphorus in the urine were less at times of hemorrhage. The loss of appetite, impairment of digestive functions, increased cell destruction, the resultant anaemia, and the excessive losses of material by the body combine to lower the resistance of the organism to the infection.

Zickgraf (1910) compares phosphorus and chlorine elimination in tuberculosis and chlorosis. He finds the average phosphorus excretion to be, as Teissier stated, lower in chlorosis than in tuberculosis; but the difference is too small, and the individual variations too great, to make possible diagnostic use of the distinction.

Mulier (1911) concludes that the phosphorus excretion in tuberculosis is not characteristic, and has no differential diagnostic value.

DEMINERALIZATION IN TUBERCULOSIS

Ott (1903) reports complete mineral and nitrogen balances with three cases of tuberculosis. He admits the presence of "demineralization" in certain cases, but finds that it is not a regular symptom.

Steinitz and Weigert (1904, 1905) analyzed the body of a tuberculous child, and compared the analysis with others by Sommerfeld on a child dead from gastrointestinal disorder, another such by Steinitz, and six analyses of new-born infants by Camerer and Söldner. They find in their study no grounds for belief in the theory of demineralization.

Amat (1906), also studying demineralization, considered the possible diminution of the phosphorus content of the body through the use of white flour as a predisposing factor to tuberculous infection. In this study mice were fed on breads made from white roller process flour, and flour ground between stones. The latter was eaten in larger quantity and produced a considerable gain in weight; the former (the roller process flour) was not eaten in quite so great quantities, and did not maintain the body weight. No evidence was submitted on demineralization.

A. Mayer (1907) studied metabolism in tuberculosis, and from complete nitrogen and mineral balances with five patients in 3-day periods draws conclusions as to demineralization. In these cases he finds a retention of calcium and phosphorus and a marked retention of chlorine. There was a slight tendency to retain potassium and a greater one to retain sodium. There was no apparent relation between the phosphorus and nitrogen balances. Mayer's positive mineral balances lead him to the belief that demineralization is not characteristic of tuberculosis.

Sarvonat and Rebattu (1910) made ash, calcium and phosphorus estimations on normal and tuberculous guinea pigs. They conclude that the total ash of the body of the tuberculous guinea pig decreases about one-tenth, this loss being due to the animal's growing thin in flesh. The absolute amount of phosphorus was less in the body of the tuberculous animals, and the proportion of phosphorus to total ash was much less, while the authors state that the phosphorus in the ash of the soft parts was sometimes the higher in the tuberculous animals. The absolute and relative calcium content of the bones of the tuberculous animals is decreased. The proportionate loss of calcium from the bones is much greater than from the soft parts. In these cases, then, there was demineralization—as, in fact, there is in starvation from whatever cause.

PHOSPHORUS COMPOUND THERAPY IN TUBERCULOSIS

Gilbert (1901) states that consumptives and neurasthenics thrive remarkably under the influence of pills containing 0.1 to 0.5 gm. lecithin. Lecithin was also administered subcutaneously in injections of 0.05 to 0.15 gm., repeated every second day. The appetite and weight increased, and no evil effects were observed, even on prolonged administration. One subject, already in a hospital for four months, gained 3.5 kg. in one month. Other details of improvement were noted.

According to Morichau-Beauchant (1901) the efficacy of lecithin therapy in tuberculosis is inversely as the stage of advancement of the disease.

Gilbert and Fournier (1901) report that egg lecithin in doses of 0.10 to 0.50 gm. per day by the mouth, or 0.05 to 0.15 gm. every other day by injection, led to general improvement, and gain in appetite, and in weight, in cases of pulmonary tuberculosis.

Claude and Zaky (1901a) found by feeding and injection experiments with lecithin, on tuberculous men and guinea pigs, increased urinary nitrogen and decreased urinary phosphorus, associated with gain in weight and general improvement. The lecithin did not affect the development of the disease. The improvement was marked in early stages of the disease, but perceptible even in those which were hopelessly advanced. See also (1901b) and (1901c).

Mouneyrat (1902a) experimented with disodium-methyl-arsenate and nucleic acid for tuberculosis. He reports results with 120 patients. The daily dose was 30 c.c. of a solution, taken in two portions, the whole containing 0.05 gm. methyl arsenate of sodium and 0.20 gm. nucleic acid from herring milt. Both red and white blood corpuscles increased rapidly, and general improvement was marked after varying periods of treatment up to a maximum of a month, the Koch bacillus disappearing from the spittle in many cases. This treatment is said to have succeeded where lecithin treatment failed.

Colombet (1902) administered this same arsenic-phosphorus compound with 33 cases of chronic tuberculosis. Two cases died; 3 did not receive benefit; the remainder were said to be improved in a notable manner, especially those having the disease in the first or second degree. Many symptoms of improvement were noted, among them diminution of phosphaturia.

Ward (1910) attempted to relieve the progressively increasing anaemia of tuberculosis by intravenous injection of nuclein-saline solution. This treatment caused a rapid disappearance of the poikilocytes, and their replacement by new and healthy erythrocytes. The data presented show that the nuclein treatment markedly increased, nearly to the normal, the haemoglobin, the number of red cells, and the specific gravity of the blood. Of the 15 cases reported, 2 died, 9 recovered and became free from tubercle bacilli, 4 were improved but not yet cured, while one refused the treatment after the first period. The solution used was composed as follows:

Approximately 6 grains of sodium triticonucleate were dissolved in each ounce of physiological salt solution, and standardized to 1 mg. organic phosphorus to each cubic centimeter. This solution was used in the quantity of 1 oz. per 20 lbs. body weight of patient.

Otolski and Biernacki (1912) made total phosphorus and phosphatid phosphorus determinations on the organs of rabbits vaccinated with dead tubercle bacilli, and compared these with similar determinations on the organs of a control rabbit. The data reported show unmistakably lower content in both these items in the kidneys, heart and lungs of the treated animals than in the control; in the livers it was lower in some cases but higher in most. The results showed a loss of lecithins and an increase of jecorins in the liver, and at the same time a marked increase in the phosphorus content of the lecithin.

Griniew (1913) has made an investigation of the quantitative differences in the lipoids and the lipoid phosphorus of several organs of guinea pigs, brought about by chronic tuberculosis. The organs were extracted consecutively with acetone, benzol, petroleum ether, alcohol and ethyl ether, and the amounts of the extracts and of their phosphorus content were recorded. Full data are given and compared in tables. We quote three condensed tables (p. 588) and a part of the author's conclusions.

Conclusions: "During tuberculous infection the chemical constitution of the cells of nearly all organs and tissues changes in its lipoidal part. This change is of qualitative as well as quantitative character. It shows itself in the diminution of the quantity of phosphorus in the lipoids and by the replacement of different forms of lipoids by each other.....

"During tuberculosis: (a) In nearly all the organs the sum of all the lipoids and the phosphorus diminishes as compared with the normal. (b) The quantity of cholesterin is increased in certain organs, diminished in others. (c) In all the organs there is less of the extracts containing lecithin. (d) In all the organs there is more of the extracts containing cephalin and myelinous materials. (e) In all the organs the diminution of the quantity of lipoidal material of the filtrate from the acetone and of the phosphorus contained in it is pronounced. (f) The quantity of materials extracted by benzol is comparatively increased in most of the organs. (g) It appears that a part of the lecithin passes into cephalin or analogous compounds. (h) The organs which suffer most in their lipoid content and in phosphorus contained there are: the lungs, the spleen, the medulla, the liver. The lungs suffer most."

LIPOIDS OF THE ORGANS OF NORMAL GUINEA PIGS
Griniew (1913)—Percent, Dry Basis

Organs and tissues	Phosphorus	Phospholipids	Lecithin		Cephalin		Phosphatids of benzol extract +Cd compounds		Lipoids of the alcohol extract soluble in water		Mixture of the lipoids of the acetone and alcohol extracts	
			Extract	P	Extract	P	Extract	P	Extract	P	Extract	P
Liver	0.3	15.9	1.2	0.022	0.5	0.011	2.7	0.03	2.04	0.03	9.5	0.18
Kidneys	0.2	14.1	1.0	0.023	0.34	0.008	3.7	0.015	4.1	0.06	5.0	0.09
Brain	0.6	31.8	0.5	0.007	2.5	0.05	2.05	0.4	5.4	0.07	2.8	0.06
Heart	0.15	12.2	0.73	0.018	0.31	0.006	1.65	0.003	3.7	0.05	5.7	0.08
Muscles	0.16	7.3	0.9	0.016	0.35	0 008	1.8	0.008	2.02	0.02	2.2	0.03
Lungs	0.2	9.7	1.56	0.03	1.1	0.038	1.83	0.006	2.3	0.05	2.8	0.07
Spleen	0.25	14.4	0.3	0.04	0.6	0.055	2.08	0.0002	7.5	0.12	3.8	0.07
Medulla	0.04	1.9	0.15	0.003	0.17	0.004	0.43	.....	0.43	0.004	0.7	0.01

(1) Apparently the heading "Lipoids" given here in the original is a mistake.

LIPOIDS OF THE ORGANS OF TUBERCULOUS GUINEA PIGS
Griniew (1913)—Percent, Dry Basis

Organs and tissues	Phosphorus	Phosphatids	Lecithin		Cephalin, myelin, and others		Phosphatids of benzol extract and of the Cd compounds		Mixture of the lipoids of the filtrate from the acetone		The portion of the alcohol extract soluble in water	
			Extract	P	Extract	P	Extract	P	Extract	P	Extract	P
Liver	0.13	9.5	0.58	0.011	0.8	0.022	1.9	0.01	3.4	0.05	2.6	0.04
Kidneys	0.09	13.7	0.97	0.03	0.73	0.0093	7.1	0.02	0.3	0.004	4.6	0.02
Brain	0.56	28.6	0.42	0.012	4.7	0.072	16.9	0.4	2.6	0.04	3.8	0.05
Heart	0.15	11.7	0.65	0.02	1.02	0.02	3.1	0.007	2.9	0.04	3.9	0.06
Muscles	0.08	9.4	0.59	0.011	0.30	0.0084	3.5	0.01	0.8	0.01	4.1	0.04
Lungs	0.14	10.0	0.37	0.011	0.4	0.007	2.1	0.015	3.1	0.03	3.2	0.07
Spleen	0.14	11.5	0.16	0.003	0.6	0.006	2.4	.....	0.8	0.006	7.5	0.1
Medulla	0.02	2.2	0.08	0.0009	0.12	0.0022	0.83	0.005	0.04	0.0005	1.1	0.01

COMPARISON OF LIPOIDS AND PHOSPHORUS IN NORMAL AND TUBERCULOUS ORGANS—(Griniew, 1913) Percent, Dry Basis

Organs and tissues	Phosphatids			Lipoids			Phosphorus		
	Normal	Pathol.	Difference	Normal	Pathol.	Difference	Normal	Pathol.	Difference
Liver	15.9	9.5	−6.4	26.6	21.5	−5.1	0.30	0.13	−0.17
Kidneys	14.1	13.7	−0.4	32.1	34.8	+2.7	0.20	0.09	−0.11
Brain	31.8	28.6	−3.2	47.9	50.4	+2.5	0.60	0.56	−0.04
Heart	12.2	11.7	−0.5	19.5	19.1	−0.4	0.15	0.15	0
Muscles	7.3	9.4	+2.1	16.8	13.6	−3.2	0.16	0.08	−0.08
Lungs	9.7	10.0	+0.3	21.1	19.7	−1.4	0.20	0.14	−0.06
Spleen	14.4	11.5	−2.9	29.8	22.4	−7.4	0.25	0.14	−0.11
Medulla	1.9	2.2	+0.3	8.7	4.9	−3.8	0.04	0.02	−0.02

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